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Proceedings of The University of Toronto Undergraduate Medical Research Day

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University of Toronto Medical Journal
Proceedings Of The University Of Toronto
Undergraduate Medical Research Day

PROGRAM

1:00-2:00 **Keynote Speaker: Dr. James Musser**
"Psychic Income Obtained from Messing Around with Bugs."
Medical Sciences Building, Room 3154

2:00-4:30 **Poster Viewing**
Medical Sciences Building, Stone Lobby

4:45-5:30 **Presentation by Winners of 1997 Research Day Competition**
Medical Sciences Building, Room 3154

Louis-Martin Boucher
Recipient of the George Brown Memorial Award-- MD/Ph.D Category, supervisor Tak Mak, Department of Medical Biophysics.
"Binding Sites of cytoplasmic effectors TRAF 1. 2 and 3 on CD30 and other members of the TNF receptor family."

Lisa Hicks
Recipient of the George Brown Memorial Award – Novice Clinical Research Category, supervisor Don Wasylenki, Department of Psychiatry.
"Clerkship training and medical student attitudes regarding effective collaboration with community agencies."

Kunuk Rhee
Recipient of the George Brown Memorial Award-- Novice Basic Research Category, supervisor Art Slutsky, Department of Medicine.
"Heat stress confers protection against ventilator-induced lung injury."

5:30-5:40 **Raffle**

5:40 **Award Presentation and Wine and Cheese Reception**
Medical Sciences Building, Ruth Kurdyak Medical Alumni Lounge

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Keynote Speaker: James M. Musser, MD, Ph.D

Assistant Professor, Department of Pathology, Microbiology and Immunology, Baylor College of Medicine, Houston, Texas

Dr. James M. Musser completed his B.Sc. in microbiology at Pennsylvania State University in 1979, and went on to graduate with a M.D. and Ph.D. in microbiology in 1988 at The University of Rochester School of Medicine in New York. His postgraduate training included research at the Institute of Molecular Evolutionary Genetics at Pennsylvania State University and a clinical/research residency in clinical pathology at the Hospital of the University of Pennsylvania in Philadelphia.

Dr. Musser is presently an Assistant Professor in the departments of pathology, microbiology and immunology at the Baylor College of Medicine in Houston, Texas. He is actively involved in medical student training, and teaches students at various levels of training including undergraduates, residents, and graduate students. Dr. Musser is the Director of the Institute for the Study of Human Bacterial Pathogenesis at the Baylor College of Medicine, Associate Chief of the Clinical Microbiology Laboratory (Methodist Hospital) and a member of the Infection Control Committee (Methodist Hospital).

Dr. Musser has received numerous awards in medicine, research and teaching including: The Rochester Academy of Medicine Prize in Internal Medicine (1988); Young Investigator Awards from both The Academy of Clinical Laboratory Physicians and Scientists and The American Society for Microbiology (1991, 1992); and the Faculty Award for Outstanding Teaching in Clinical Pathology (1994-1995). He has been invited as a guest speaker to many conferences both in the United States and internationally. His professional affiliations include: Academy of Clinical Laboratory Physicians and Scientists; American Society for Investigative Pathology; American Society for Microbiology; and Genetics Society of America. He is presently on the editorial boards of: *Journal of Bacteriology, Emerging Infectious Disease*, and *Tubercle and Lung Disease*. He also reviews manuscripts for other journals including: *Infection and Immunity, Journal of Clinical Investigation, Journal of Clinical Microbiology, Journal of Immunology, Journal of Infectious Diseases*, and *New England Journal of Medicine*.

Dr. Musser's own research laboratory is presently funded by grants from, the American Heart Association, National Institutes of Health, and Advanced Research Program/Advanced Technology Program. His laboratory consists of postdoctoral fellows, Ph.D. candidates, as well as undergraduate students. Dr. Musser has been an author in over one hundred peer-reviewed articles, numerous book chapters, and has given numerous presentations at both national and international conferences.

Dr. Musser's laboratory currently addresses four main research topics, all relating to re-emerged bacterial pathogens. One area of interest centers on *Streptococcus pyogenes* (Group A *Streptococcus*), the agent responsible for several infections including rheumatic fever and the recently described toxic-shock syndrome. He is investigating the molecular mechanisms responsible for disease resurgence, the role in virulence of an extracellular cysteine protease that activates interleukin-1ß precursor, and potential use of this protease to develop an efficacious vaccine. The role of this cysteine protease in the pathogenesis of necrotizing fasciitis ('flesh eating disease') is also under study. A second major research area is development of rapid and unambiguous molecular strategies to diagnose mycobacterial infections, and identify drug-resistant strains of *Mycobacterium tuberculosis*. Large-scale automated DNA sequencing techniques are being used. A third research topic in his laboratory is the study of molecular and social epidemiology of all *M. tuberculosis* cases in Houston. Finally, the fourth area of investigation by Dr. Musser is the role that human genetics play in the susceptibility to tuberculosis.

Representative Publications

Musser JM. (1996). Molecular population genetic analysis of emerged bacterial pathogens: selected insights. *Emerging Infect.* Dis. 2:1-17.

Musser JM, Stockbauer K, Kapur V, and Rudgers GW. (1996). Substitution of cysteine 192 in a highly conserved Streptococcus pyogenes extracellular cysteine protease (interleukin-1ß convertase) alters proteolytic activity and ablates zymogen processing. *Infect. Immun.* 64: 1913-1917.

Sreevatsan S, Pan X, Zhang Y, Kreiswirth BN, and Musser JM. (1997). Mutations associated with pyrazinamide resistance in pncA of Mycobacterium tuberculosis complex organisms. *Antimicrob. Agents Chemother.* 41: 636-640.

Pai S, Esen N, and Musser JM. (1997). Routine rapid Mycobacterium species assignment in a clinical microbiology laboratory based on species specific allelic variation in the 65-kildalton heat shock protein (hsp65) gene. Submitted to *Arch. Pathol. Lab. Med.*

Lukomski S, Sreevatsan S, Amberg C, Richardt W, Woischnik M, Podbielski A, and Musser JM. (1997). Inactivation of Streptococcus pyogenes extracellular cytsteine protease significantly decreases mouse lethality of serotype M3 and M49 strains. Submitted to *J. Clin. Invest.*

Message from the Dean

Arnie Aberman, MD, FRCPC, Dean of Medicine

Welcome to the 1998 Annual Medical Student Research Day. This is an important day for our Faculty, because it provides an opportunity for our undergraduate medical students to showcase the wide spectrum of research projects they have completed, often during summer fellowships with Faculty of Medicine supervisors. These projects range from investigation of basic cellular activity to studies of clinical applications in hospitals and community involvement, revealing the many career pathways open to today's medical students.

Taking a research project form concept to completion provides undergraduates with a stimulation learning experience, giving them the opportunity to discover if they have the self-discipline, dedication and creative thinking required to be a successful investigator. As Dean, I am proud to say that many of our undergraduate medical students do have these qualities. Take a look at their research projects and you will see what I mean. Research is an important tradition in our Faculty and we continue to be inspired by the impact that research has on the practice of medicine. It is my hope that many of the students involved in today's Medical Student Research Day will continue that tradition. Congratulations to all the participants - and many thanks to the faculty members who made this year's event possible.

Arnie Aberman, MD, FRCPC
Dean, Faculty of Medicine

Message from the Vice-Dean

Andrew D. Baines, MD, Ph.D, FRCPC, Vice-Dean, Education

The Faculty of Medicine Undergraduate Medical Student Research day provides an opportunity for students to display the results of their research. Each summer approximately 100 medical students receive scholarships through the Faculty of Medicine enabling them to work on projects in basic science laboratories and clinical investigative settings. Their research follows diverse paths from basic molecular biology to clinical outcomes and community health. Approximately 40% of the students who apply are funded and present their work on Research Day. Selection is based on scholarship and merit of the proposed research. Students in the summer research program and the MD/Ph.D. program also present their work at Medical Student Research Day. The top-rated students in the categories of basic and clinical research, receive an all-expense paid trip to the Annual Medical Student Research Forum (USA) in Galveston, Texas, in April, representing our Faculty. In addition the Department of Medicine supports the top-rated student (in either the clinical or basic science category), supervised by one of its members, to attend the same meeting.

Why do students wish to extend their professional training into the realm of biomedical research? There are many reasons including scientific curiosity and extension of previous engagement in research. More than 30% of students now entering Medicine at Toronto hold graduate degrees. Nonetheless for many of the students, whose abstracts are contained in this journal, their first taste of research came after they entered the medical program. All the research presented at Research Day has been carried out while students are enrolled in the undergraduate medical program or the MD/Ph.D. program. Many of these students have and will contribute to scientific papers published in peer-reviewed journals. Some will seek future career development as clinician-scientists, by entering graduate or post-graduate research programs during or after clinical specialty training. The Faculty of Medicine at the University of Toronto is a major focus of basic and clinical investigation in Canada. The 12th annual Medical Student Research Day shows how effectively our medical students take advantage of this rich learning environment.

Students participating in research day have taken time out of a demanding professional training program to prepare and present their posters. Health care professionals engaged in research are challenged to maintain a balance between clinical and investigative responsibilities. The students who participate in Research Day begin to experience this sometimes difficult, yet highly rewarding, duality. The posters displayed at the Research Day demonstrate the fruits of their self-discipline, dedication and creativity.

The students and Faculty are indebted to the Medical Student Committee who worked so hard and efficiently in the planning and preparation for Research Day.

Andrew D. Baines, MD, Ph.D, FRCPC
Vice-Dean, Education
for the Research Day Coordinating Committee

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Biochemistry

B1

The Oxidation of Human Low Density Lipoprotein by Superoxide. David A. Hall*, Mary Jane Young, Keith U. Ingold. Steacie Institute for Molecular Sciences, National Research Council of Canada, 100 Sussex Dr., Ottawa, Ont., K1N 0R6

The oxidation of low density lipoprotein (LDL) has been implicated as an initiator of atherosclerosis. The mechanism of this oxidation has not yet been elucidated but superoxide must be considered as a possible oxidant. Until recently a convenient source of superoxide that could deliver this species in a controlled manner under physiological conditions has not been available. The recent invention of SOTS-1 has however provided such a source of superoxide and thereby the means to investigate the role of superoxide in the oxidation of LDL. Micelles of 1-palmitoyl-2-linoleoyl-sn-glycero-3-phosphocholine (PLPC) and human LDL were reacted with SOTS-1 generated superoxide under physiological conditions. The products of the reactions were analyzed by HPLC with post-column chemiluminescence detection. Both PLPC and human LDL were readily oxidized by superoxide. The oxidation of LDL was inhibited by superoxide dismutase but not by catalase. The results are discussed with regards to the role of superoxide in atherogenesis.

Cardiovascular

C1

THE IMPACT OF GENDER ON CARDIAC HYPERTROPHY AND WORK CAPACITY. C. Cserti*, J. Wallen, M. Belanger, C. Wittnich. Departments of Surgery & Physiology, Faculty of Medicine, University of Toronto, Canada M5S 1A8. *funded by a grant from the Heart & Stroke Foundation of Ontario*

Cardiac hypertrophy occurs in response to chronically increased work load. Gender impact on hypertrophy and its correlation with alterations in afterload (diastolic pressure-DP;mmHg) and work capacity (systolic pressure-SP;mmHg) was studied. **Methods:** Age-matched male & female normotensive (WKY) and hypertensive (SHR) rats were either intact or gonadectomized (neutered). Neutered females either received no treatment, estrogen replacement (Est) or the pseudoestrogen, tamoxifen (Tam). Cardiac hypertrophy was determined using heart to body weight (hrt/bw;mg/g) ratio. **Results:** For any given DP, hrt/bw was greater($p<0.05$) in females than males. Neutering females removed this difference while Est returned values to those seen before and Tam had lowest values (eg: row 1, table).

sample	female	male	neuter female	Est	Tam
hrt/bw (DP,100)	4.1	3.6	3.4	4	3
SP (hrt/bw, 3.7)	133	188	196	184	211

In most groups, hrt/bw increased with increasing DP however, neutered males lost this response. In the absence of estrogen, a significantly greater response to increasing DP occurred as measured by slopes of hrt/bw vs DP (slope, 10^{-3} mg/g/mm Hg: females 4.7, males 6.7, neuter female 10, Est 2.2). For any given hrt/bw, SP was lowest in females when compared to males. Neutered females lost this difference while Est did not return these values and Tam SP was even greater (eg: row 2, table). Increasing hrt/bw resulted in significantly higher SP in all groups except neutered males, where again the response was lost as measured by slope of SP vs hrt/bw.

Thus gender differences, due to estrogen, do exist in the heart's response to increasing afterload and its work capacity.

C2

HORMONE REPLACEMENT THERAPY USE IN HIGH RISK WOMEN AT A CANADIAN ACADEMIC CENTRE.

Michelle R Wise*, Donna E Stewart, Peter Liu, Beth L Abramson
Divisions of Cardiology and Women's Health, The Toronto Hospital, Faculty of Medicine, University of Toronto, Canada.

Background: Post-menopausal Hormone Replacement Therapy (HRT) in women at risk for Coronary Artery Disease (CAD) is beneficial. It is recommended that women at increased risk of CAD should consider HRT. We evaluated HRT use in high risk women at an ambulatory cardiology clinic. We hypothesized that HRT use would be low, but higher than in the general population.

Methods: A retrospective survey of HRT use and factors influencing this decision was conducted on all women who attended the Cardiology Clinic at The Toronto Hospital from 1996 to mid-1997.

Results: Seventy nine post-menopausal women were seen at the clinic (data on 71 to date). Fifteen (19%) were currently on HRT, 56 (71%) were not, and 14 (18%) had taken HRT in the past. Of non-users, 25% had possible contraindications. Four of 36 (11%) women with established CAD were taking HRT. The mean age of the women currently on HRT was 60±9 years and of non-users was 71 ±10 years (users vs non, $p=0.03$). HRT use was documented in 13 (16%) charts. Five women were on HRT but there was no chart documentation.

Conclusion: Few high risk women at this centre were currently taking HRT. There is a striking lack of documentation in patient charts surrounding this issue. The data support the need for further review of current practice patterns in women with CAD.

C3

Outcomes of Atrial Tachyarrhythmias after the Fontan Operation

A. Ghai*, L. Harris, D. Harrison and S. Siu. Toronto Congenital Cardiac Centre for Adults, The Toronto Hospital, University of Toronto, Canada. M5G 2C4.

The Fontan operation is a palliative procedure done to alleviate cyanosis in some patients with complex congenital heart disease. Atrial tachyarrhythmias is a frequent complication of the Fontan operation. The purpose of this study was to review the incidence and outcome of atrial tachyarrhythmias in patients (pts) with complex congenital heart defects who underwent Fontan surgery between 1977 and 1994 at the Hospital for Sick Children. Data was obtained on 87 pts (41 males [47%]; 56 females [53%]) through retrospective chart review of all available hospital records at the Toronto Congenital Cardiac Centre. The patients reviewed had either tricuspid atresia (48) or a univentricular circulation (39). 68 pts had a Fontan shunt between the right atrium (RA) and pulmonary artery (PA), while 19 pts had a shunt between the right ventricle (RV) and PA.

Results: 34 of the 87 (39%) pts had symptomatic sustained atrial arrhythmias (atrial fibrillation, atrial flutter or supraventricular tachycardia) following their Fontan procedure. Gender, pt age at surgery and clinical events were compared between the arrhythmia and arrhythmia-free group.

	No Atrial Arrhythmia	Atrial Arrhythmia	p
Male Gender	38%	62%	0.028
Fontan Age (mean ± SD) yrs	16±8	20±10	-
Cardiac Thrombus developed	2%	24%	0.002
Thrombus developed after arrhythmia	-	21%	-
Pulmonary Embolism + Cardiac Thrombus developed	9%	26%	0.035
Heart failure after arrhythmia	-	38%	-
Mean Survival Time (yrs)	17.7	17.2	NS

Conclusions: Pts who develop atrial tachyarrhythmias are more likely to develop cardiac thrombus with or without pulmonary embolism. Thirty-eight percent of pts who develop an atrial tachyarrhythmia, will later develop heart failure. The development of atrial arrhythmias does not significantly alter mean survival time.

C4

TEN-YEAR FOLLOW-UP OF ADULTS WITH REPAIRED TETRALOGY OF FALLOT USING SERIAL RADIONUCLIDE ANGIOGRAPHY

Veena Guru*, James T. Elliott, Michael A. Gatzoulis, David Harrison, Erwin Oechslin, Samuel Siu, Gary Webb, William G. Williams, Peter Liu, Peter McLaughlin. Toronto Congenital Cardiac Centre for Adults, The Toronto Hospital, University of Toronto.

Background. Right ventricular dysfunction contributes to long-term outcome in patients with repaired tetralogy of Fallot (rTOF). We employed serial radionuclide angiograms (RNA) to examine changes in right ventricular (RV) and left ventricular (LV) function in adults with rTOF.

Methods. We reviewed 10-yr records (1987-1997) of 97 patients (55 men) followed in our clinic with rTOF (mean age at repair 12.9±10.6 yrs, mean age at follow-up 37.6± 9.9 yrs) and at least 2 RNAs.

Results. At the study conclusion most patients remained well (NYHA class I-80%, II-15%, III-5%). Eleven patients had clinical arrhythmias (7 atrial, 4 VT); 1 died suddenly. Thirteen patients had elective right ventricular outflow tract (RVOT) reoperation (pulmonary valve replacement-10, relief of RVOT obstruction-3). No change in RV and LV function was seen (mean interval 5.7 ± 2.1 yrs between RNAs).

	LVEF rest	LVEF exercise	RVEF rest	RVEF exercise
First RNA	54.0±12.1	59.2±12.8	37.7±11.8	40.1±13.3
Last RNA	55.5±12.4	60.8±13.6	39.9±10.8	42.9±12.6

*Mean values (ejection fraction %)±SD, Δ between first vs. last RNA not significant

In the reoperation group preoperative RV function did not differ from the remainder and did not change after surgery.

Conclusion. This group of closely followed rTOF pts remained well over 10 yrs with a low incidence of arrhythmias and stable RV and LV function, despite a relatively large number of reoperations. Aggressive intervention for right-sided hemodynamic disturbances may have contributed to this outcome. Preserved ventricular function may herald a favorable long-term outlook in this group.

C5

TRANSCATHETER BALLOON DILATION VERSUS SURGERY FOR NATIVE AORTIC COARCTATION IN CHILDREN—A CLINICAL DECISION ANALYSIS

Amish Parikh*, M. Srivamadevan, Lee N. Benson, Brian W. McCrindle. Division of Cardiology, Department of Pediatrics, Faculty of Medicine, Univ. of Toronto, Toronto.

Background. Balloon dilation of native aortic coarctation (CoA) remains controversial. We sought to assess utilities related to out-comes of balloon dilation vs. surgery in a formal decision analysis.

Methods. A clinical decision tree with probabilities of outcomes and complications was developed using contemporary results reported in 20 published series (813 balloon dilations, 1458 surgeries of native CoA in children). Preferences for outcomes (utilities) were assessed in modified standard gamble interviews of 10 pediatric cardiologists, 14 fellows, 3 clinic nurses and 4 cardiac surgeons at a single institution. Final utility scores ranged from 0 (death) to 1 (perfect procedure) for isolated CoA in a 2-10 yr old.

Results. Initial preferences were for balloon in 30 and surgery in 1 (surgeon). After interviews and decision tree analyses, mean final utility scores favored balloon (0.988±0.012) vs. surgery (0.962±0.036; p=.0001) with only 1 cardiology fellow having a higher score for surgery. There were no significant differences between the groups of respondents regarding final scores, although the surgeons were more clearly a draw (mean difference 0.008±0.007; p=.25). Sensitivity analysis favored surgery only if the chance of major complication with balloon exceeded 56%, or mortality with balloon exceeded 6%. The chance of aneurysm or restenosis did not alter the decision favoring balloon.

Conclusion. Based on systematic analysis of outcomes and complications and their value, transcatheter balloon dilation of isolated native CoA in children is preferable to surgery.

C6

ETIOLOGIES OF STROKE DURING VALVE SURGERY; RELATION TO DECREASED PREVALANCE OF STROKE OVER TIME?

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Stroke is a major cause of morbidity and mortality following valve surgery. The prevalence of penoperative stroke over the past 15 years, however, has decreased. The purpose of this study was to examine whether trends in stroke etiologies may account for the decreased prevalence of stroke from 1982 to 1996 **Methods:** Retrospective review of prospectively gathered data on 6717 consecutive patients undergoing valvular procedures at the Toronto Hospital from 1982 to 1996. Stroke was defined as non-transient central nervous system deficit. Patients were divided into 3 groups according to date of operation: 1982-86, Group 1 (n=2330); 1987-91, Group 2 (n=2275); and 1992-96 Group 3 (n=2112) Chart review was undertaken of patients who developed stroke (n = 223) The strokes were classified under the following possible etiologies (1) aortic atherosclerotic emboli; (2) cardiogenic emboli, (3) septic emboli; (4) penoperative hypotension, (5) carotid vascular disease, (6) air embolism; (7) unknown **Results:** Stroke occurred in 4 0% of Group 1 patients, 3 3% in Group 2, and 2 6% in Group 3 (p=.029) Multivariable logistic regression analysis revealed the following predictors of stroke (odds ratios and 95% C.I in parentheses) (1) time interval of operation (1982-86, OR 2.4, 1 6 to 3 4, 1987-91 OR 1.5, 1 1 to 2 2), (2) endocarditis (OR 2.4, 1.5 to 3.9); (3) urgent timing (OR 2.2, 1 6 to 3 0), (4) age > 74 (OR 2 1, 1 4 to 3.2), (5) concomitant coronary bypass (OR 1.8, 1.3 to 2 4), (6) reoperation (OR 1.4, 1 0 to 1.9) Systematic chart review revealed the following frequencies of stroke etiologies: aortic atherosclerotic emboli 8%(Group 1), 9% (Group 2), 12.5% (Group 3); cardiogenic emboli 30% (Group 1), 27% (Group 2), 27% (Group 3), septic emboli 0% (Group 1), 9% (Group 2), 12 5% (Group 3), perioperative hypotension 12% (Group 1), 0% (Group 2), 16% (Group 3), carotid vascular disease 4% (Group 1), 9% (Group 2), 0% (Group 3); air embolism 8% (Group 1), 0% (Group 2), 2% (Group 3), unknown 38% (Group 1), 45% (Group 2), 30% (Group 3) **Conclusion:** Systematic chart review revealed the following etiologies of perioperative stroke (in decreasing order of frequency) cardiogenic emboli, aortic atherosclerotic emboli, perioperative hypotension, septic emboli, carotid vascular disease and air embolism.The cause was not determined in 40% of patients. However, the comparison of stroke etiologies between time groups did not explain the diminished stroke prevalence over the past 15 years

C7

Determination of Ideal Fibroblast Donor Age on Angiogenesis and Improvements in Heart Function in Scarred Myocardium Michael Lekas, Zhi Qiang Jia, Richard D. Weisel and Ren-Ke Li. Division of Cardiovascular Surgery, The Toronto Hospital

Cardiomyocyte loss due to ischemic injury is largely irreversible. Cell transplantation may represent a novel modality of stimulating angiogenesis and preventing the progressive loss of heart function and death of cardiomyocytes. In a previous study (UTMJ 74:CV6, 1997), allogenic fetal fibroblast transplantation into scarred myocardium resulted in diffuse angiogenesis with enhanced survival of native myocardial cells. Grafting of fetal fibroblasts also prevented ventricular remodelling mediated dilatation and scar thining observed in non-transplanted animals in response to extensive myocardial scarring. The aim of the present study is to determine the donor age of grafted fibroblasts that will optimize angiogenesis and heart function.

METHODS: Experiments were conducted in 30 male, Sprague-Dawley rats with cryogenically scarred myocardium randomly divided into three groups: a control group (CG, n=10) and two transplant groups receiving cultured adult (3 month) and juvenile (2 week) fibroblasts (TA and TJ respectively, n=10) injected directly within myocardial scar tissue. Injections of saline (CG) and cells (TA and TJ) were performed two weeks post cryoinjury. Post transplantation all rats will be maintained with daily cyclosporine injections. Eight weeks post-cryoinjury heart function (systolic, diastolic and developed pressures) in both groups will be measured using a Langendorff preparation. Angiogenesis will be assessed histologically and scar areas and volumes measured by computed planimetry.

POSSIBLE OUTCOMES: Adult fibroblast transplantation that results in enhanced angiogenesis and survival of myocardial cells within scarred myocardium may represent a new revascularization modality of autologous transplantation without the potential of graft rejection. Absence of enhanced blood vessel formation within scarred tissue with adult fibroblast transplantation will require investigation for fetal derived angiogenic growth factors.

C8

IDENTIFICATION OF DIFFERENTIALLY EXPRESSED GENES IN CARDIAC HYPERTROPHY BY LARGE-SCALE ANALYSIS OF EXPRESSED SEQUENCE TAGS. D.M. Hwang*, C.Y. Lee, C.C. Liew. The Cardiac Gene Unit, Department of Laboratory Medicine and Pathobiology, The Centre for Cardiovascular Research, University of Toronto, Toronto, Ontario, Canada, M5G 1L5

Cardiac hypertrophy is an adaptive response to chronic hemodynamic overload and an early step in the progression to heart failure. Underlying the hypertrophic response are alterations in gene expression; hence, the identification of genes which exhibit differential expression in cardiac hypertrophy should provide insight into the molecular mechanisms of hypertrophy and heart failure. To characterize gene transcription and identify new genes that are over-expressed in cardiac hypertrophy, we analyzed 65,666 expressed sequence tags (ESTs), from 11 human heart cDNA libraries. ESTs matching to known genes were categorized according to function, allowing for analysis of general transcriptional patterns. This revealed a proportional increase in transcripts related to cell/organism defense ($p<0.001$) and a decrease in transcripts related to cell structure and motility ($p<0.001$) in hypertrophic hearts compared to normal adult hearts. More detailed *in silico* expression analysis of 4,366 known genes represented in the data set identified 30 genes significantly over-expressed in cardiac hypertrophy ($p<0.0005$), at least 9 of which had previously been identified by *in vitro* methods and one-third of which represented genes involved in cell/organism defense. Thirty-one weaker candidates for differential expression were also identified ($p<0.01$). Overall, this combined EST-based approach to characterizing gene expression in cardiac hypertrophy resulted in observations largely compatible with current understandings of cardiac hypertrophy, while generating novel findings. These results suggest that methods for mining information generated by the Human Genome Project may hold tremendous potential for investigating questions of cardiovascular biology and medicine.

C9

HVJ-LIPOSOME MEDIATED GENE TRANSFER WITH A PLASMID ENCODING DECOY RNA CONTAINING THE 3' UNTRANSLATED REGULATORY REGION (3'-UTR) OF FIBRONECTIN (FN) mRNA INHIBITS NEOINTIMAL FORMATION IN THE DUCTUS ARTERIOSUS (DA). C.A.E. Mason*, M. Rabinovitch. Division of Cardiovascular Research, Hospital for Sick Children, University of Toronto.

We have previously shown that migration of smooth muscle cells (SMC) during neointimal formation in the late gestation ductus arteriosus (DA) depends on increased fibronectin synthesis, regulated at the post-transcriptional level by interaction of the RNA binding protein LC3 with an AU rich element (ARE) in the 3'-untranslated region of FN mRNA. In cultured SMC transfected with 'decoy' chloramphenicol acetyl transferase (CAT) expression plasmid in which the 3'-UTR of CAT was replaced with the 3'-UTR of FN (pECE-CAT-FN_{wt}), we demonstrated enhanced CAT activity compared to controls transfected with a construct containing a mutated ARE in the FN 3'-UTR (pECE-CAT-FN_{mut}), and that endogenous FN synthesis was inhibited, with a concomitant change in SMC phenotype to that of a less motile cell. We hypothesized that transfection of the fetal lamb DA *in utero* with pECE-CAT-FN_{wt} would similarly sequester LC3, reduce FN and potentially other LC3 regulated proteins which direct the migratory phenotype, and thereby inhibit neointimal formation. Gene transfer was therefore performed on 90 day gestation fetal lambs in utero, by lateral thoracotomy, transient isolation of the DA and injection of HVJ (37000 hemagluttinating units)-liposomes containing pECE-CAT-FN_{wt} or pECE-CAT-FN_{mut} (200 μg DNA). The CAT constructs permitted immunohistochemical identification of transgene activity. Lambs transfected with pECE-CAT-FN_{wt} survived to term (145 days) and delivered spontaneously with patent DA. There was no evidence of SMC migration or neointimal formation and CAT activity was evident throughout the media indicating persistent transgene expression. In control lambs (untreated, saline injected or transfected with pECE-CAT-FNmut) full neointimal formation was observed at term. Thus we have developed an effective way to biologically engineer a cardiovascular developmental process in the DA by manipulating a program which regulates SMC motility; this may have therapeutic implications for duct-dependent congenital heart defects.

Clinical Pharmacology

CP1

ADVERSE DRUG REACTIONS IN CHILDREN: AN 11-YEAR REVIEW OF HEALTH CANADA DATA. **ML Kohn*, SR Knowles, NH Shear. Department of Clinical Pharmacology, Sunnybrook Health Science Centre, University of Toronto, Toronto, Ontario, Canada.**

Approximately 2-5% of children prescribed medication will experience an adverse drug reaction (ADR) Limited information is available regarding this problem.

Data was obtained from the Adverse Drug Reaction Monitoring Division of Health Canada. All suspected ADRs experienced by children and reported between 1985 and 1995 were included in our analysis. Drugs were coded using the Anatomical Therapeutic Chemical (ATC) Classification System whereas reaction types were coded according to the World Health Organization (WHO) Adverse Reaction Terminology Analysis was performed using descriptive statistics and χ^2-tests.

A total of 1545 reactions were included in the analysis The mean age of the children was 6.1 ± 5 4 years. 35% of the reactions occurred between 1 and 6 years of age An average of 1 17 drugs were suspected in causing the reported ADRs The drug classes most commonly implicated were. general anti-infectives for systemic use (75%), nervous system agents (10%) and respiratory system agents (4%) The most common classes of reactions included: cutaneous eruptions (49%), vaccination reactions (16%) and whole body disorders (14%)

Serious reactions were reported in 305 (19.7%) cases. Eight children died A slight preponderance of serious versus non-serious reactions were reported in females (55 vs 47%), ($p<0.001$) Cutaneous reactions were reported in only 15% of serious events compared with 59% of non-serious reactions, ($p<0.001$) Cefaclor induced serum sickness-like reaction and vaccination reactions were documented in 8 and 17%, respectively, of serious cases

ADRs are a widespread problem which affect children of all ages In some instances, significant morbidity and even mortality results The majority of reactions in this study caused only minor morbidity Nevertheless, systematic reviews of pediatric ADRs may help to reveal otherwise unidentified or preventable trends.

Emergency Medicine

EM1

CLINICAL PREDICTORS OF OUTCOME FOR PATIENTS WITH HEMODYNAMICALLY SIGNIFICANT BRADYCARDIA IN THE PREHOSPITAL CARE SETTING. C. Idestrup *, P. Datta, and B. Schwartz. Division of Emergency Medicine and Division of Prehospital Care. Sunnybrook Health Science Center. University of Toronto. Canada.

Objective: To determine clinical predictors of poor outcome for patients with hemodynamically significant bradycardia in the prehospital care setting.

Methods: Level II/III Metro Toronto Ambulance paramedic reports. from March. 1996 to February. 1997. were manually screened for patients with a heart rate (HR) ≤ 60 beats per minute. blood pressure (BP) ≤ 90 mmHg. and one or more of chest pain. shortness of breath. decreased consciousness. or evidence of congestive heart failure Trauma or pregnant patients were excluded. Patient outcome (i.e. improved or not improved) upon hospital arrival was based on a validated subjective score. Differences in clinical characteristics between patients who improved and those who did not were analyzed by chi-square ($p<0.01$ was considered significant).

Results: We identified 252 patients. With medical or supportive therapy. 119 (47%) improved There was a statistically significant difference in outcome for patients whose HR responded to supportive therapy (defined as an increase > 5 beats per minute) (64% improved) compared to patients with non-responsive HR (43% improved) ($p<0.01$). Also. there was a statistically significant difference in outcome for patients with a BP which responded to supportive therapy (increase of ≥ 5 mmHg) (72% improved) compared to patients with non-responsive BP (32% improved) ($p<0.01$). In contrast. there was no difference in outcome based on gender. sinus vs. non-sinus rhythm or QRS width

Conclusions: HR and BP non-responsiveness are clinical predictors of poor outcome for patients with hemodynamically significant bradycardia in the prehospital setting.

EM2

GLUCAGON VERSUS ORAL GLUCOSE FOR EMERGENCY PRE-HOSPITAL TREATMENT OF HYPOGLYAEMIA. M. Klompas*, C. Mazza. Emergency Services Prehospital Care Division, Sunnybrook Health Sciences Centre, University of Toronto, Canada, M4N 3M5.

We compared the effectiveness of oral glucose gel and glucagon s.c. for emergency pre-hospital treatment of patients with confirmed hypoglycaemia (blood glucose <4.0 mmol/l) using a retrospective, historical cohort study design. We hypothesised that in the brief period that paramedics are with patients before transferring them to definitive care, neither treatment has sufficient time to take effect. For an initial six month period, Metro Toronto Level 1 Paramedics treated all hypoglycaemic patients with up to 20g of D-glucose p.o. according to standardised protocols. Over the subsequent six month period, paramedics used identical protocols to treat hypoglycaemic patients except that 1.0 mg glucagon s.c. was used instead of oral glucose. Each patients' blood glucose levels and Glasgow Coma Scale (GCS) scores were assessed prior to treatment and at regular intervals after treatment. Preliminary results suggest that patients given glucagon showed a higher increase in blood glucose and level of consciousness by the time of final paramedic assessment (transport times did not differ between cohorts). In addition, proportionately fewer problems (contraindications, difficulty administering medication, refusal of treatment) were encountered when giving patients glucagon compared to oral glucose (5% vs 12%, P=0.007, chi-square test). We conclude that glucagon is a more effective treatment for emergency pre-hospital care of hypoglycaemia.

Change in Blood Glucose Concentration (mmol/l)

	mean change ± SD	n	unpaired Student t-test
Glucose gel	0.67 ± 1.7	232	P<0.0001
Glucagon	1.6 ± 1.3	90	

Change in Level of Consciousness (Glasgow Coma Scale)

	initial GCS (median)	final GCS (median)	n	Mann-Whitney test
Glucose gel	12	14	257	P<0.0001
Glucagon	11	15	95	

Endocrinology

EN1

NOVEL NEUROENDOCRINE INTERACTIONS GOVERNING SECRETION OF GLUCAGON-LIKE PEPTIDE-1. A.S. Rocca*, P.L. Brubaker, Department of Physiology, Faculty of Medicine, University of Toronto, Canada, M5S 18A.

Plasma levels of glucagon-like peptide-1 (GLP-1) rise rapidly after nutrient ingestion, suggesting the presence of a proximal signal regulating GLP-1 release from the L cells of the ileum. Glucose-dependent Insulinotropic Peptide (GIP) has been shown to be one such proximal signal, however, the dependence of GIP on gastrin-releasing peptide, a neuromodulator, indicated a possible role for the nervous system in this proximal-distal loop. Investigations into the proximal signal were conducted in an *in situ* model of the rat gastrointestinal system. Infusions of corn-oil into a 10 cm segment of duodenum isolated by loose ligation (to ensure that luminal contents did not progress to the ileal L cell) increased the secretion of GLP-1 in parrallel with that of gut glucagon-like immunoreactivity (gGLI) ($r=0.96$, $P<0.05$). Left cervical vagotomies significantly decreased basal levels of gGLI secretion from 205 $\pm$ 10 pg/ml in controls to 113 $\pm$ 9 pg/ml in vagotomized animals ($P<0.001$). Infusion of fat significantly raised gGLI secretion compared to saline infusions in ligated and transected segments of duodenum, reaching peak values of 130 $\pm$ 39 pg/ml and 132.03 $\pm$ 37 pg/ml above basal ($P<0.05$), respectively. However, peak secretion was significantly delayed when the gut was transected as compared to ligation alone (19 $\pm$ 4 vs 6 $\pm$ 1 min, respectively; $P<0.05$). Bilateral subdiaphragmatic vagotomy in conjunction with gut transection abolished the fat-induced rise in gGLI secretion ($P<0.001$). Stimulation of the distal end of the celiac branch of the subdiaphragmatic vagus nerve stimulated basal secretion of gGLI by 71 $\pm$ 14 pg/ml ($P<0.01$). Supraphysiological infusion of GIP significantly increased gGLI secretion in both sham and hepatic branch vagotomized animals by 123 $\pm$ 32 pg/ml ($P<0.01$) and 96 $\pm$ 25 pg/ml ($P<0.05$), respectively. Although infusion of GIP at physiological levels into sham vagotomized animals significantly increased gGLI secretion, by 40 $\pm$ 6 pg/ml ($P<0.01$), selective hepatic branch vagotomy abolished the GIP-induced gGLI secretion ($P<0.05$) and decreased the basal level of gGLI secretion ($P<0.05$). Therefore, these experiments demonstrate that the release of GLP-1 from the ileal L cell in response to fat is regulated by a complex neuroendocrine loop involving afferent and efferent vagus nerves and the duodenal hormone GIP.

Haematology

HM1

AUDIT OF PLATELET TRANSFUSIONS, ADVERSE REACTIONS, AND PREMEDICATION AT PRINCESS MARGARET HOSPITAL. D. Grynspan*, T. Panzarella, B. Patterson, J. Meharchand, Division of Oncologic Pathology Princess Margaret Hospital and Faculty of Medicine, University of Toronto

Platelet transfusions are given to thrombocytopenic patients to stop or prevent hemorhage. This includes patients with leukemia and lymphoma, patients undergoing bone marrow suppressive chemotherapy, as well as patients receiving bone marrow transplants. Several types of platelet products are given including : single donor platelets collected by plasma apharesis, random pooled platelets, and HLA matched platelets. A potential complication is the occurrence of nonhemolytic platelet transfusion reactions including: chills, rigors, fever, hives, and hypotension. Methods used to reduce the incidence of platelet transfusion reactions include: plasma depletion of 3, 4, and 5 day old random pooled platelets, and premedication of the patients.

Audits were carried out in both the summers of 1996 and 1997. Data obtained includes: patient demographics and diagnosis, type and age of product , use of premeds, presence of adverse reactions, and type of adverse reactions.

Our most significant finding is a reduction in total percent of reactions from 22% in 96 to 17% in 97, with a concomitant *decrease* in the amount of premedication used. One potential contributing factor is the increased proportion of single donor versus random pooled platelet given. Also, in-house staff education seminars regarding administering premeds appropriate to the type of reactions previously encountered may have increased the effectiveness of the premedications used while decreasing the overall use of premeds.

Health Care Delivery

HD1

DECISION MAKING IN MATURE ADULTS: GENDER DIFFERENCES. B.Crawford*, D. E. Stewart, M. Meana. Women's Health Program, The Toronto Hospital, Faculty of Medicine, University of Toronto.

Studies have shown that women are less likely to receive several specific medical interventions including organ transplantation, cardiac diagnostic studies and coronary artery bypass surgery. This may result in higher morbidity and mortality for women. This study tests the hypothesis that gender differences in treatment decisions made by older adults explain gender differences in treatment rates for specific interventions.

A self report questionnaire using hypothetical situations, treatment choices and influencing factors was designed based on literature review and interviews with key informants. The questionnaire was administered to community groups of adults over the age of 50 in urban and rural setting in Ontario. Data analysis used Chi-square, t-tests and the Bonferroni correction.

Preliminary results (n=259) revealed no significant gender differences in decisions made or factors affecting decisions.

Gender differences in treatment decisions do not explain gender differential in utilization rates for these procedures. In the absence of outcome data or patient choice data to support gender differential utilization rates, clinicians need to carefully consider their assumptions in the provision of specific interventions to male and female patients. Further research on gender differences in medical treatment is recommended.

HD2

PROSPECTIVE STUDY OF PATIENT SATISFACTION IN A TEACHING HOSPITAL PREADMISSION UNIT. A.R. Burns*, J. Bradley, K. Karkouti. Department of Anaesthesia, The Toronto Hospital, General Division, University of Toronto, Canada.

With the current climate in today's hospitals of restructuring, cost control, and downsizing, the need for more efficient and effective use of hospital resources has become imperative. To this end hospitals have shifted services to an outpatient basis; hence the surgical preadmission unit (PAU) was born. Currently, at our tertiary care teaching hospital, more than 80% of all surgical patients are assessed in our PAU. Despite our volume and acuity of patients the effectiveness of this unit has been demonstrated by a cancellation rate below the accepted benchmark (1.6%). As a further assessment of quality assurance we designed this study to measure patient satisfaction with our PAU program To do so, standardized pre- and post-operative questionnaires were developed, and patients living in the greater metropolitan area were randomly selected, within the unit, over a 10 week period. All patients were interviewed by a single investigator. To analyze the data descriptive statistical methods were used. Sixty-nine patients completed the pre-operative questionnaire with 51 of those completing the post-operative questionnaire. Overall, 80% of patients were satisfied. Our waiting time was less than expected by patients and over 80% felt that the pre-operative teaching offered was adequate. Pre-operative anxiety was low, and remained unchanged after their PAU visit. Suggestions to improve our unit came from 47% of patients, ranging from hospital organization to pre-operative teaching (*e.g.* pain control and anaesthesia related side effects). Overall, patient satisfaction with our unit was acceptable. Pre-operative teaching was shown to be adequate, and, although we did not remove patient's anxiety regarding their experience, we found they had little to begin with. Despite the positive outlook patients had on our unit many still offered suggestions, confirming for us there are still ways we can improve.

HD3

HOW DO FAMILY PHYSICIANS MANAGE THEIR ETHICAL ISSUES? A PILOT STUDY. D.T. Farkas*, M. Keatings, E. Etchells. Joint Centre for Bioethics, University of Toronto, Canada, M5G 1L4.

Family physicians are constantly faced with making ethical decisions that can impact on their provision of health care. The purpose of this project was to identify which methods or resources family physicians use to help them manage these ethical issues. Furthermore, this study attempted to identify which additional resources family physicians would find helpful if implemented.

A survey instrument was designed, and distributed to several groups of family physicians. The first part asked these physicians about the frequency, the difficulty, and the importance of their ethical problems, and the extent to which their medical education had trained them to deal with these issues. The second part of the survey concentrated on the methods or resources these family physicians were using, or would like to be using, to help them manage their ethical problems. Finally, some demographic data was also collected.

Nine family physicians agreed to complete the survey. The results were incomplete due to the many limitations of the study. The sample size was small, and some of the answer choices were ambiguous. What could be seen is that family physicians do believe they have ethical problems, which are difficult to solve, and for which they are inadequately trained. In addition, though there are presently some resources which these physicians find helpful in managing these ethical problems, there are many more resources they would find helpful if implemented.

While this study provided little information of immediate value, it is useful in helping to develop future studies. From the feedback given by respondents, several changes have been made to the survey instrument. This new survey could be mailed to a cross section of family physicians across Ontario. The results of that study could provide useful information to those planning Health Care resources in Ontario. Hopefully new resources could be added to the current resource network, thereby helping Ontario family physicians better manage their ethical problems.

HD4

IMPACT OF LEUKEMIA ON PEDIATRIC PATIENTS AND THEIR FAMILIES : EVALUATION OF SUPPORT IN THE HOSPITAL FOR SICK CHILDREN VS. PRINCESS MARGARET HOSPITAL. A. Cheng*, J. Wright RN, J. Meharchand MD, S. Weitzman MD. Department of Hematology/Oncology, Hospital for Sick Children and Department of Medicine, Princess Margaret Hospital, University of Toronto, Canada

Leukemia is a disease whose effects span far beyond the physical well-being of the patient. This project was designed to study the effect of leukemia on the emotional and psychological well-being of the patient and his/her family. Problems encountered by leukemic patients and their families were elicited to determine the issues needed to be addressed by the support network. Support services at the Princess Margaret Hospital (PMH) and the Hospital for Sick Children (HSC) were assessed and recommendations were made for improvement based upon feedback provided by patients and their families. The population studied included adolescents aged 16 to 19 at PMH and children aged 8 to 12 at HSC with a diagnosis of acute lymphoblastic leukemia and undergoing the maintenance phase of their treatment. Questionnaires were distributed to the patients and one parent, family drawings were done by the patients and parents, and interviews were performed with patients, parents, nurses, social workers and physicians. This study revealed that adolescents, children and their families undergo significantly different changes in character, attitude and behaviour as a consequence of acute lymphoblastic leukemia. Additionally, the support network at HSC was found to be much better established compared to PMH. Recommendations for improvement at both hospitals were made in hopes of improving the emotional health and social well being of leukemic patients and their families.

HD5

CARDIAC REHABILITATION: WHAT MIGHT INCREASE PATIENT PARTICIPATION? Lani Lieberman*, Donna Stewart and Marta Meana. Women's Health Program, The Toronto Hospital, University of Toronto, Canada, M5G 2C4.
OBJECTIVE: To investigate the barriers and incentives that are most influential in the decision of coronary patients to participate in cardiac rehabilitation programs (CRPs) and to suggest strategies for overcoming these barriers.
DESIGN: Patient survey.
SETTING: Cardiac Rehabilitation Center (CRC) at a university tertiary care hospital.
PARTICIPANTS: One-hundred and twenty-nine attenders and sixty-one referred non-attenders at a CRP.
METHODS: Questionnaires outlining potential influential factors, which may have altered decisions to engage in CRPs, were constructed from a literature review and advice from key informants. Surveys were administered to English speaking CRP attenders and non-attenders.
MAIN FINDINGS: Physician recommendation was reported to be the most important factor in influencing a patient's decision to participate in CRPs, followed by encouragement from family members. Concomitant medical conditions and transportation problems were stated to be the two most important reasons that patients chose not to attend the program. Women rated their children as more influential in their decision making process than did men.
CONCLUSIONS: The decision about whether or not to participate in CRPs appears to involve several factors. As physician recommendations continue to be the single most important factor in motivating both men and women, family doctors are well placed to encourage participation in CRPs.

Health in the Community

HC1

PREGNANT OR PARENTING WOMEN WITH DRUG ADDICTIONS: FACTORS AFFECTING TREATMENT MAINTENANCE. L.K. Hicks* & M. Leslie. Faculty of Medicine, University of Toronto, Canada, M5G 1X8.

Recently, considerable public attention has been focused on the issue of illicit drug use during pregnancy. Interestingly however, while there is a large body of literature which documents the prevalence of drug use during pregnancy and outlines its harmful effects, very little is known about pregnant/parenting substance users themselves. The objective of this study was to characterize a population of pregnant and/or parenting substance users with respect to demographic information, primary addiction, history of abuse, mental health problems and other important parameters. Additionally, the study sought to identify client factors correlated with poor treatment maintenance. A retrospective file analysis was performed using data from a Toronto agency which targets pregnant/parenting women with addictions. The files of all clients seen between May, 1995, and March, 1997, were analyzed (n=109). The results of this study suggest that pregnant and parenting women with drug addictions represent a very marginalized and vulnerable population: 89% of the sample was unemployed, 69% were single mothers, 71% had less than high school education, and 49% had unstable living arrangements. The most commonly cited primary addiction in this study was crack/cocaine (54%). Most women had more than one child (avg = 2.3) and history of multiple pregnancies. A large majority of the sample (90%) was involved with a child protection agency. Sexual abuse, physical abuse and mental health problems were extremely common in this population. Two client factors were identified which were significantly correlated with poor treatment maintenance: (1) having less than high school education ($p=0.005$) and (2) citing crack/cocaine as one's principle addiction ($p=0.008$).

HC2

PRIMARY HEALTH CARE AMONG THE REFUGEE AND IMMIGRANT POPULATION IN TORONTO. K.G. Stel*, Dr. B. Stubbs. Department of Family and Community Medicine, The Toronto Hospital, University of Toronto, Canada, M6J 3S3.

Culturally-defined perceptions of health and illness inevitably affect patient care in urban areas of the Western world whose ethnic tapestries are increasingly rich and diverse. Medical training must draw special attention to the health sequelae of migration in favourable or adverse circumstances. In particular, the family doctor as a primary care giver must be aware of these issues, ranging from economic hardship to bodily trauma, which may confront him or her daily when working among the refugee and immigrant population. Clinical encounters with refugees and immigrants, interviews with key informants serving primarily the East African and South East Asian populations, and literature reviews yielded a tangible outcome in the form of a Cross-Cultural Medicine Manual for the family practice residents at The Toronto Hospital. Sensitivity in communication is the first step that allows clinicians to enter the journey with their patients. Many physical, emotional, and spiritual trials may be disguised beneath culturally-defined restraints and behaviours. Hence, armed with sensitivity, compassion, and an awareness of one's own worldview, issues including mental health, women's health, culturally-specific health patterns, screening of the migrant adult and child, and tropical health prevention and treatment may be explored. Healing may become a reality when physical - but more importantly, the emotional and spiritual - needs of the individual in his or her community are met. The common ground of human experience and an undefined longing for acceptance and love - regardless of culture - will allow the sensitive clinician to meet the refugee or immigrant patient in his or her place of need.

HC3

KNOWLEDGE AND PERSONAL RISK ASSESSMENTS OF SEXUALLY TRANSMITTED DISEASES (STDs) IN A COLLEGE POPULATION. J.S. Lok*, M.Meana, A.M. Cheung. Women's Health Program, The Toronto Hospital, University of Toronto, Canada, M5G 2C4.

OBJECTIVES: The purpose of this study was to assess awareness, knowledge and personal risk estimates for a variety of STDs in a college population, as well as to determine whether there are gender differences in these variables. HYPOTHESES: 1)That college students' awareness and knowledge of STDs vary depending on the STD and that this variance does not correlate with actual incidence rates. 2)That students rate their personal risk for any one STD as significantly lower than actual incidence rates. 3)That there are gender differences in students' assessment of their own personal risk for any one STD, with men making lower risk estimates than women. METHODOLOGY: 154 male and female university students, aged 18-29, completed a questionnaire which consisted of identifying STDs and completing a true/false quiz to evaluate knowledge and assess perception of average population and personal risk of these STDs. RESULTS: There was a high level of awareness of the STDs overall, with the highest being HIV (correctly identified as an STD by 99.4%) and the lowest being HPV (70.9%). Similarly, both men and women rated their perceived knowledge of HIV to be the highest and claimed to be the most ignorant about HPV. The quiz showed that actual knowledge was again best for HIV and worst for chlamydia and HPV. There was a positive correlation between perceived knowledge and actual knowledge ($r=731$, $p<.01$). There were no gender differences in performance on the test as a whole or with respect to specific STDs. Women assessed the risk of an average person their age to be higher than did men ($F=9.3$, $p<.003$); however there were no gender differences in assessment of personal risk, as had been hypothesized. Both men and women perceived their personal risk to be lower than the average populaiton risk, and this difference was statistically significant for all STDs ($t=14.41$, $p<.0001$). There was, however, no gender difference in the discrepancy between average risk and personal risk assessment. CONCLUSIONS: Level of knowledge is lowest for the most common STDs, even among this highly educated population of mostly science and medical students. There were no gender differences in knowledge or risk perception in this group of college students, as has been suggested by other studies.

HC4

SHAKEN BABY SYNDROME: FOLLOW-UP EVALUATION OF DETERMINANTS IN CHILD DEVELOPMENT V. Selvanandan*, M. Mian, M.Balthazor, J.Rosenfield. The Suspected Child Abuse and Neglect Team and The Child Development Centre. The Hospital for Sick Children, University of Toronto, Canada. M5G 1X8.

Shaken Baby Syndrome (SBS) has severe physical, emotional and developmental consequences for children who have experienced this form of abuse. In order to ensure that they realize the full extent of their developmental potential, survivors of SBS require proper rehabilitation and care. The purpose of this study was to examine the environment in which children given the diagnosis of SBS are growing and developing to determine if the needs of the children and their caregivers are being adequately met. The sample (n=12) was obtained from the Suspected Child Abuse and Neglect database at the Hospital for Sick Children which contains 45 children with the diagnosis of SBS. Data regarding biological, psychosocial and health care determinants of development was gathered through semi-structured telephone interviews with caregivers, and developmental status was determined by administration of the Vineland Adaptive Behvaioural Scales. Four children in the sample were found to have adequate adaptive levels, 1 had a moderately low adaptive level , 3 had mild to moderate developmental deficits and 4 had moderate to severe deficits. The medical and rehabilitation needs of the children were well-matched to the services they were receiving in all areas except that of speech and language in children with severe global developmental deficits. Caregivers were less satisfied with supports and services for themselves and desired more respite care, more information regarding SBS at time of diagnosis as well as education on resources in the community for themselves and their children. Close follow-up of all children regardless of current level of functioning is required to identify emerging or worsening deficits and to assess changing needs in rehabilitation and therapy.

Immunology

IM1

THE SHP-1 TYROSINE PHOSPHATASE REGULATES SPONTANEOUS AND ACTIVATION INDUCED T CELL APOPTOSIS. Ally-Khan Somani*, Jinyi Zhang and Katherine Siminovitch. Departments of Medicine, Immunology and Medical Genetics and Microbiology, University of Toronto, Samuel Lunenfeld Research Institute, Mount Sinai Hospital,Toronto, Ont., M5G 1X5

Based on recent data implicating the SHP-1 tyrosine phosphatase in Fas-mediated signaling cascades, we investigated the role for SHP-1 in modulating induction of T cell apoptosis. Analysis of peripheral T lymphocytes from SHP-1-deficient viable motheaten (me^v) mice revealed markedly increased survival of these cells in vitro compared to wild-type cells. Increased survival of the me^v T cells was associated with upregulated expression of Bcl-2 protein, the latter being 2-3 fold higher in the me^v than in wild-type cells. When stimulated with ConA and IL-2, the me^v cells showed hyperproliferative responses and enhanced MAP kinase activation compared to similarly treated wild-type cells. Moreover, apoptotic cell death of activated T cells stimulated in the absence of exogenous IL-2 was also higher in the me^v compared to normal cells. By contrast, no differences were detected between the me^v and wild-type cells with respect to Fas/FasL-induced apoptosis or with respect to signaling through the CD28 and CTLA 4 receptors. Together these data indicate the association of SHP-1 deficiency with enhanced survival of "resting" T cells and suggest that the progressive accumulation of T cells in the me^v periphery reflects increased lifespan of these cells and/or their enhanced response to antigenic stimulation, but is not due to a defect in Fas/FasL signaling. In addition, the demonstration that SHP-1-deficient activated T cells are aberrantly sensitive to growth factor deprivation-induced cell death, but show intact Fas signaling suggests that SHP-1 is not required for Fas-mediated signaling in T cells, but, depending on the costimulatory circumstances, inhibits the signaling cascades linking TCR stimulation to proliferation or apoptosis.

IM2

ALLO-IMMUNIZATION IN THE CONTEXT OF AN HIV VACCINE STRATEGY
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Gene products of the major histocompatibility complex (MHC) are incorporated into the HIV-1 envelope as the virion buds from the host cell surface. Studies using simian immunodeficiency virus (SIV) infection of macaques has demonstrated that previous immunization with *uninfected* human cells or purified MHC proteins can provide protection from challenge with live SIV that has been grown in human cells expressing the same MHC alleles. These xenogeneic immunization experiments (*i.e.* human MHC into macaques) show that anti-MHC immune responses are important to consider when designing vaccines for viruses such as SIV or HIV.

To better determine the role of anti-MHC responses in the human HIV vaccine context, we have endeavoured to study allo-immunization. Plasmid DNA immunization was used to elicit both B- and T-cell allo-immune responses to defined human class I MHC gene products (or human leukocyte antigens, HLAs) in a transgenic mouse model system. cDNA expression vectors, encoding either HLA-A2 or HLA-B27, were constructed for use as plasmid DNA immunogens. These vectors were made to also encode for the co-stimulatory molecule B7-2. Mice transgenic for either HLA-A2 or HLA-B27 have also been bred for intramuscular and genegun challenge with the different human class I MHC expression vectors, or for intraperitoneal challenge with cells from the different HLA transgenic animals.

Both syngeneic and allogeneic immunizations (*e.g.* HLA-A2 immunogens, either plasmid DNA or spleen cells, into either HLA-A2 or HLA-B27 mice, respectively) were conducted to determine if this type of immunization breaks tolerance and is able to induce antibody responses specific for the class I HLA immunogen. Anti-HLA Ab responses were induced in the allogeneic immunizations, while no anti-self-HLA Ab response was detected in the syngeneic immunizations, in both the DNA- and cell-immunized mice. Xenogeneic immunizations (*i.e.* HLA immunogens into C57BL/6 mice) were conducted and showed that immunizing with either HLA-encoding DNA or HLA-expressing cells also elicited strong anti-HLA Ab responses. In addition, we measured for xenogeneic CTL responses and found that DNA vectors that encoded for both HLA and B7-2 were better at inducing CTL responses, at levels comparable to cellular immunizations. We were able to generate specific anti-human class I HLA responses in both human HLA transgenic and non-transgenic mice. Immunization with DNA immunogens can elicit both B- and T-cell mediated responses that are comparable, but somewhat more variable, to those made by cellular immunogens. Human class II HLA DNA constructs have also been made and shown to be immunogenic in C57Bl/6 mice. Results of non-human primate macaque immunizations with these constructs to determine its safety and immunogenicity will also be presented. The encouraging results in the transgenic mouse model indicate that plasmid DNA immunization with MHC-encoding vectors merits further consideration as an alternative and/or complementary approach to the design of an HIV vaccine. (supported by the MRC)

ID1

A COMPARISON OF BACTERIAL SWABS AND QUANTITATIVE BIOPSIES OF CHRONIC SKIN ULCERS AND THEIR USE PRIOR TO LIVING SKIN EQUIVALENT (APLIGRAF™) APPLICATION.

Joline Chen*, R.Gary Sibbald. Department of Medicine (Dermatology), Women's College Hospital, Faculty of Medicine,University of Toronto.

Backgrounds The use of living skin equivalent (Apligraf™) for chronic wounds healing is promising. To optimize the healing, we assessed the effect of bacterial infection on the outcome of living skin equivalent.

Objective To compare bacterial swabs and quantitative bacterial biopsies of chronic skin ulcers in detecting bacterial infection and in predicting the outcome of living skin equivalent

Methods Nine patients with chronic skin ulcers had one to three Apligraf™ applications each. A surface swab and a quantitative skin biopsy were taken prior to Apligraf™ application. The primary take rate of the Apligraf™, the degree of wound healing, and the bacteriology of the wounds were evaluated.

Results Only one of the 14 pairs of swabs and skin biopsy specimens results agreed. 2 of 5 patients with organism count $>10^5$ had primary partial take whereas 6 of 9 patients with organism count $<10^5$ had partial take. In total, 8 of the 14 Apligraf™ applications had a partial take and eventually seven of the nine patients' wounds improved.

Conclusion The findings of surface swabs do not reliably correlate with those of quantitative skin biopsies and surface swabs do not predict the organism load in the deep tissue infection. The indication of quantitative skin biopsy for regular clinical use and in the application of skin substitutes requires further investigation.

ID2

IMPACT OF LENGTH OF CATHETER TIP (CT) ON INTERPRETATION OF SEMI-QUANTITATIVE CULTURE (SQC) RESULTS IN A PEDIATRIC POPULATION. Tsippora Shainhouse*, Dr. Anne G. Matlow. Departments of Pediatric Laboratory Medicine and Microbiology, The Hospital for Sick Children, University of Toronto, Canada, M5G 1X8.

Laboratory confirmation of catheter-related bacteremia (CRB) relies on Maki's SQC method[1] established in adults, where it has a sensitivity of up to 85%.[2] Researchers have advocated colony counts higher and lower than Maki's recommended positive cut-off of >15 colonies/CT. There is no literature on the impact of his second recommendation - that a 5-7 cm length of CT be submitted for culture. Using a retrospective analysis of 355 laboratory records and corresponding charts, we investigated the relationships between SQC result, clinically-diagnosed CRB and CT length in a pediatric population. The sensitivity of a positive SQC result was 49.25%, 60.53% and 68.42% for CTs <5, 5-7 and >7 cm, respectively, indicating a trend towards increased sensitivity with increased CT length. Irrespective of CT length, these values fall far short of the 85% sensitivity observed in adults. Although we are not advocating submission of catheter tips >7 cm in length for SQC, our data suggest that the importance of length of CT submitted for culture may have been inadequately recognized. These data suggest that Maki's guidelines for colony count and CT length, may both be inappropriate in the pediatric population. [1]Maki, D.G., C.E. Weise and H.W Sarafin. 1977. A semiquantitative culture method for identifying intravenous-catheter-related infection. New England Journal of Medicine 296(23): 1305-1309. [2]Collignon, P. and R. Munro. 1988. Limitations of semiquantitative culture method for catheter culture. Journal of Clinical Microbiology 26: 1076 (letter).

ID3

MAC PROPHYLAXIS: APPLICATION OF GUIDELINES I.E. Salit and S. Minor*. Immunodeficiency Clinic, The Toronto Hospital, University of Toronto, Canada, M5G 2C4.

Introduction: MAC prophylaxis (prx) has been recommended at CD_4 counts <100 (clinical trials), <75 (USPHS 1995 guidelines), or <50 (USPHS 1997 guidelines). It is uncertain how widely this recommendation is followed.

Methods: Pts. with a CD_4<100 (332 pts.) were included. We collected information on demographics, MAC prx, concomitant therapy and the development of MAC. A questionnaire was also given to 100 pts. to determine their knowledge of HIV, MAC and MAC prx.

Results: MAC prx was used at any time in 72/225 (32%) pts. with CD_4<50, 82/294 (28%) pts. with CD_4<75 and 87/332 (26%) pts. with CD_4<100. The first regimens were: rifabutin 73 pts. (84%), azithromycin 10 pts. (11%), clarithromycin 3 pts. (3%). Rifabutin was stopped in 44 (66%) of these pts. usually due to drug interactions or adverse reactions. Of these 44 pts. who discontinued rifabutin, 14 (32%) switched to azithromycin and 3 (6.8%) switched to clarithromycin. Rifabutin usage decreased and azithromycin increased with the advent of protease inhibitors; currently, only 46/332 (13.8%) of pts. with CD_4<100 are on MAC prx. The regimens are: rifabutin in 24 pts. (52%), azithromycin in 20 pts. (43%) and clarithromycin in 2 pts. (4.3%). The mean number of months of follow-up was 32.9 months. MAC developed in 13% of all pts., 14% who had received prx and 13% who did not. MAC occurred in 18% who had stopped their prx. Patients' knowledge about MAC significantly correlated with CD_4 <100, use of MAC prx or MAC therapy. Only 38% who were no on MAC prx, had had MAC explained to them.

Summary: MAC prx in not commonly used because of the use of numerous other medications, drug interactions and lack of knowledge of the condition by pts.

ID4

THE ADHERENCE AND IMMUNOGENIC PROPERTIES OF THE *ENTAMOEBA DISPAR* Gal/GalNAc LECTIN. Dylan R. Pillai* and Kevin C. Kain. Institute of Medical Science, University of Toronto, 1 King's College Circle, Toronto, ON, CANADA M5S 1A8 and Tropical Disease Unit, Division of Infectious Diseases, Department of Medicine, The Toronto Hospital, 200 Elizabeth Street, Toronto, ON, CANADA, M5G 2C4.

Amebiasis is the third leading cause of parasitic disease in humans and is estimated to cause significant morbidity in approximately 50-100 million individuals worldwide. *Entamoeba histolytica* is the pathogenic protozoan associated with invasive disease. In this organism, adherence and cytolysis of target cells is mediated by a Galactose/*N*-Acetyl Galactosamine-specific surface lectin. *Entamoeba dispar* is morphologically identical but genetically distinct to *E.histolytica*. While *E.dispar* infection is asymptomatic in humans, we have recently shown that this protozoan also transcribes a gene encoding the functional subunit of the Gal/GalNAc lectin. In order to further characterize functional differences between the *E.histolytica* (Hgl2) and *E.dispar* (Dhgl2) Gal/GalNAc lectin, we have cloned the coding sequence of heavy and light subunits from both species into mammalian expression vectors. *In vitro* transcription and translation, with and without microsomes, followed by immunoprecipitation has been used to characterize the structural and immunological properties of the subunit. In this way, we have shown that the pathogenic lectin heavy subunit (from *E.histolytica*) contains a β2-integrin epitope which is absent in the non-pathogenic lectin (from *E.dispar*). Amino acid sequence comparison with other integrins identified a MIDAS domain present in the lectin; this motif is known to mediate metal-ion dependent adhesion. To confirm that the intergin domain was present on the surface of amebic trophozoites, indirect immunofluorescence was carried out. Functional characterization of the β2-integrin epitope contained within the lectin clearly demonstrates that mAb MHM23 which is directed against human β2-integrin can inhibit adherence of *Entamoeba* trophozoites to target cells which contain ICAM-1 (the putative receptor for β2-integrin). Conversely, the MHM23 is unable to inhibit adherence to the same target cells lacking only in the expression of ICAM-1. Further assays using immobilized human ICAM-1 indicated that amebic trophozoites as well as the radiolabelled lectin alone are able to bind to this receptor in a manner consistent with an adhesion role mediated by the β2-intergin domain contained within the Gal/GalNAc lectin. Taken together, the data suggest not only the presence of a β2-integrin domain on the Gal/GalNAc lectin but also that this adhesion domain has functional relevance to the adherence properties of this parasite. The increased invasiveness and hematogenous spread of the pathogenic strain (*E.histolytica*) as compared to the non-pathogen (*E.dispar*) might be explained by the presence of this integrin domain which mediates adhesion to ICAM-1 residing on endothelial cells. Experiments assessing the adherence of amebic trophozoites to bovine endothelial cells (BAECs) confirm that the ameba are able to adhere to these cells in a MHM23-inhibitable manner.

MB1

PROTEIN-PROTEIN INTERACTIONS OF RAS-GRF2, A NOVEL ACTIVATOR OF RAS PROTO-ONCOGENES. Neil P. Fam* and Michael F. Moran. Banting and Best Dept. of Medical Research and Dept. of Molecular and Medical Genetics, Faculty of Medicine, University of Toronto, Canada M5G 1L6.

Mutationally activated alleles of ras proto-oncogenes are acutely transforming and are prevalent in a broad spectrum of human tumors. p21 Ras proteins function as GTPases, cycling between inactive GDP-bound and active GTP-bound conformations. Ras proteins play a pivotal role in transducing signals from extracellular molecules such as growth factors, immune antigens and integrins into intracellular pathways that lead ultimately to nuclear transcriptional activation. Conversion of Ras proteins into an activated GTP-bound state able to bind effector proteins is catalyzed by guanine nucleotide exchange factors in response to many extracellular stimuli. Recently, we isolated cDNAs encoding Ras-GRF2, a multidomain 135-kDa protein containing a C-terminal Cdc25-related domain that stimulates guanine nucleotide exchange on Ras in vitro and in vivo. The N-terminal region of Ras-GRF2 contains features common to various signaling proteins including two pleckstrin homology domains and a Dbl homology region. Ras-GRF2 also contains an IQ motif which is required for its apparent constitutive association with the calcium sensor calmodulin. Transient expression of Ras-GRF2 in kidney epithelial cells stimulates GTP binding by Ras and potentiates calcium ionophore-induced activation of mitogen-activated protein kinase (ERK1) dependent upon the IQ motif. Calcium influx causes Ras-GRF2 subcellular localization to change from cytosolic to peripheral, suggesting a possible mechanism for controlling Ras-GRF2 interactions with Ras at the plasma membrane. Human kidney epithelial cells overexpressing Ras-GRF2 are morphologically transformed and grow in a disorganized manner with minimal intercellular contacts, suggesting a possible role in carcinogenesis. Although GRF2 has been shown to mediate calcium-induced Ras activation, the endogenous signalling pathways involving GRF2 remain largely unknown. To gain insight into GRF2 signalling, an affinity purification approach was employed to identify novel GRF2-binding proteins.

MB2

REGULATION OF APOPTOSIS AND CELL CYCLE BY STRESS-ACTIVATED PROTEIN KINASES/JUN-N-TERMINAL KINASES (SAPKS/JNK)

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Stimuli that stress cells, including inflammatory cytokines, ultraviolet light and DNA-damaging chemotherapeutic drugs and heat shock lead to cellular responses such as growth arrest, repair, and programmed cell death (apoptosis). Recently a cytoplasmic signaling cascade that is activated following cellular stress has been identified. This pathway consists of the stress-activated protein kinase and the upstream activating kinases SEK and MEKK.

In order to evaluate the physiological role of SAPK in cellular response to stress, we have introduced a dominant inhibiting SEK mutant into RIF and Rat1 fibroblasts. These cells are refractory to SAPK activation following a variety to stresses. In addition, these cells are resistant to the cytocidal effects of heat shock, UV irradiation and DNA-damaging agents. Because cell death in many systems has been linked to aberrant regulation of cell cycle regulatory molecules, we tested the hypothesis that SAPK may have a role in ce!" cycle control. Using cell lines expressing dominant-negative SEK and cell lines expressing inducible activators of SAPK, we demonstrate that SAPK has a role in the regulation of cell cycle at G1/S. The examination of the downstream effectors of SAPK may suggest therapeutic approaches to alter cellular response to chemotherapy.

MB3

OCI-5 AND IGF-2: PARTNERS IN DEVELOPMENT AND GROWTH?

Howard H. Song*, Wen Shi, and Jorge Filmus, Medical Biophysics, Sunnybrook Health Science Centre

OCI-5 is a cell surface heparan sulfate proteoglycan that was first identified as a gene involved in intestinal morphogenesis. Recently, the human of OCI-5 homologue (95% amino acid sequence identity), glypican-3 (GPC3), was found to be mutated in patients with the Simpson-Golabi-Behmel Syndrome (SGBS). SGBS is an X-linked disorder characterized by, most notably, pre- and postnatal overgrowth, and a wide range of visceral and skeletal dymorphisms. Premature perinatal death is also commonly observed in patients, as well as an increased predisposition to developing Wilms' tumours. It has been recently suggested that hGPC3 interacts with insulin-like growth factor-2 (IGF-2) and that this interaction regulates IGF-2 activity. We report here however that we have transfected OCI-5 into two different cell lines, and we have not been able to detect an interaction between the OCI-5 proteoglycan produced by the transfected cells and IGF-2. Despite our findings, there are two major reasons to still believe that OCI-5 is involved in IGF-2 signaling: (1) there are many clinically overlapping features between SGBS and another overgrowth disease known as the Beckwith-Wiedemann Syndrome (BWS), whose etiology is most widely accepted as being caused by the overexpression of IGF-2; (2) Wilms' tumour development is associated with the disregulation of IGF-2 expression. We are therefore proposing that OCI-5/GPC3 regulates IGF-2 signaling indirectly through interactions with other components of this signaling pathway.

MB4

THE THIRD WW DOMAIN OF rNEDD4 INTERACTS WITH PROLINE-RICH REGIONS OF NOVEL 16-DAY MOUSE EMBRYO EXPRESSION LIBRARY PROTEINS.

P.C. Henry*, D. Rotin. Division of Respiratory Research, The Hospital for Sick Children, University of Toronto, Canada, M5G 1X8.

We have previously identified the WW domains of the rat homologue of Nedd4 (rNedd4) as a specific binding partner for the second of two PY motifs (XPPXY) found in the β and γ subunits (βP2 and γP2 respectively) of the amiloride sensitive epithelial sodium channel (ENaC) protein. Mutation of the βP2 and γP2 regions have been linked to the etiology of a rare genetic disorder, Liddle's syndrome, characterized by a hyperactive ENaC causing pseudohyperaldosteronism and systemic hypertension. Thus, the Nedd4 WW domain-PY motif interaction has been implicated in regulation of the ENaC membrane protein.

The third WW domain (WW3) of rNedd4 protein was used to screen a 16-day mouse embryo λEX*lox* phage expression library. Two true positive clones were identified, the library DNA inserts were isolated, nucleotide sequenced and converted into amino acid sequence. Both clones were found to encode novel protein regions that included two PY motifs in addition to proline-rich (non-PY motif) sequences.

Similar collaborative studies using the WW2 domain of rNedd4 identified several binding partners containing the PY motif. These results strongly suggest a conserved protein-protein interaction between the Nedd4 WW domains and PY motifs which may play an important functional role in the cell.

MB5

CONSTRUCTS FOR INDUCIBLE VEGF EXPRESSION IN THE RETINAL PIGMENT EPITHELIUM: A POTENTIAL TRANSGENIC MODEL OF CHOROIDAL NEOVASCULARIZATION IN AGE RELATED MACULAR DEGENERATION.

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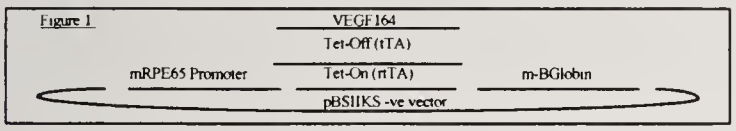
The leading cause of irreversible blindness in the developed world is from choroidal neovascularization (CNV) due to age-related macular degeneration (AMD). There is currently no effective treatment for AMD. Laser therapy results in a 50% recurrence rate and visual results are poor. Basic studies to understand the mechanisms of disease are necessary to derive and test potential treatments and understand the physiologic basis of the disease. Animal models to date have been unsatisfactory in this regard. Vascular endothelial growth factor (VEGF) is postulated to be the major mitogen for angiogenesis and agent for vessel permeability in CNV. VEGF and its receptors are upregulated in laser-induced models of CNV. The retinal pigment epithelium (RPE) expresses VEGF at high levels, possibly promoting angiogenesis and causing macrophage migration and secretion of VEGF. The purpose of this project was to create constructs for a transgenic murine model of inducible VEGF expression in the RPE. **Methods:** The tetracycline inducible gene expression system (Tet-On and Tet-Off), the promoter for the mRPE65 gene, which codes a product expressed only in the RPE in mice, the 164 isoform of VEGF and a m-BGlobin intron were used. A novel method of site directed mutagenesis was performed on the RPE65 segment using time and concentration altered Bal31exonuclease digestion after restriction enzyme (RE) digest and followed by linker ligation-digestion to remove a duplicate RE site. The m-BGlobin gene will also be mutated. The segments were then prepped in their respective vectors, purified, orientation and site maps confirmed with RE digests, cleaved and gel purified. The rtTA and tTA transactivators and the 164 isoform of VEGF will then be spliced to the mutated RPE65 promoter and m-BGlobin in a pBSIIKS -ve vector. (VEGF164 is the main isoform expressed in models of CNV to date). **Results:** Figure 1 is a schematic representation of the 3 final spliced constructs. The insertion and correct orientation of the constructs is confirmed by various strategic RE digests. Constructs will be used to produce transgenic mice which may potentially become a tetracycline inducible RPE VEGF expression model of CNV in AMD.



MB6

MAPPING THE DOMAINS REQUIRED FOR HOMEODOMAIN AND NUCLEAR RECEPTOR PROTEIN INTERACTIONS.

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Charles H. Best Institute, Banting and Best Department of Medical Research, University of Toronto, Canada, M5G 1L6.

Nuclear hormone receptors and homeodomain proteins constitute two protein superfamilies required for the regulation of major developmental processes in all complex organisms. Work performed previously in the lab showed that two members of the two protein families are obligate cofactors. The *Drosophila* gene *fushi tarazu (ftz)*, encodes a homeodomain protein (Ftz), which is required for the formation of alternate segments in the developing embryo. The orphan nuclear receptor, Ftz-F1, which is deposited into the egg during oogenesis, is required for this activity. It was hypothesized that Ftz and Ftz-F1 interact directly via conserved domains, and that similar domains may mediate interactions between other members of these two gene families. The objectives of my research were to demonstrate this direct interaction (which would then be subsequently verified *in vivo*) and to map the regions that are required and sufficient. This involved making a series of deletions in both proteins, resolving the deleted polypeptides on gels, and transferring to membranes. The membranes were then probed with the labelled partner protein, and after washing, were autoradiographed. The deletions showed which regions were sufficient and which were required, for specific binding. For Ftz, it was found that the N-terminal region is sufficient; this includes the amino acid sequence LRALLT, the only conserved residues in a distantly-related flour beetle Ftz protein, which I also showed bound to *Drosophila* Ftz-F1. This motif (LXXLLX) is found in other hormone receptor cofactors as well. For Ftz-F1, the interaction domain is in or near the ligand binding domain. Interestingly, this region contains leucine-rich motifs which, in related proteins, are bound by other LXXLLX-containing cofactors. These results are the first example of a direct interaction between two very important protein families, and the mapped interaction domains are likely to be conserved in other family members.

MB7

Rapid, high-level protein production using DNA-based Semliki Forest virus vectors.

David P. DiCiommo* and Rod Bremner.
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Methods for the expression of high levels of protein have important implications both clinically and in a basic research context. Molecular biology laboratories require pure proteins in large amounts (mg) in order to study function, and vaccines that have therapeutic value are needed in similar quantities. Large amounts of protein can be produced in bacteria, but often the product is inactive or insoluble and lacks modifications that only occur in eukaryotic cells. Viruses have evolved mechanisms that permit high expression of their own proteins, so several expression systems have been developed that exploit this feature to synthesize a protein of choice. One such system is based on the Semliki Forest Virus (SFV). The SFV expression system has several advantages over the more popular baculovirus system, including faster production of recombinant virus and a wider host cell range. However, SFV has not become the vector of choice for protein expression, primarily because the current system requires in vitro manipulation of RNA. We have modified the existing vectors so that the system is wholly DNA-based. Both the replicon vector, encoding SFV polymerase and the protein of interest, and the helper vector, encoding viral structural proteins, were modified so the expression was RNA polymerase II-dependent. Transfection of the modified replicon plasmid alone generated approximately 20-30 pg of protein per cell, which is comparable to that obtained with the original RNA-based approach, and 20-30-fold more than obtained from a simple expression vector driven by the small promoter. These high expression levels were dependent of the activity of SFV replicase, which amplifies replicon RNA. The SFV-based vectors also generated 10-20-fold more protein than a related plasmid based on the Sindbis virus, a difference which we attribute to the stronger promoter used in our vector. Cotransfection of replicon and helper vectors generated viral titers around 10^{9} infectious particles per ml. A single electroporation, plated on one 10 cm plate, generated enough virus to produce 0.5 mg of protein. These vectors significantly enhance the utility of the SFV expression system.

ME1

THE UNBIASED MIND: A POSSIBLE RESOURCE FOR MEDICAL PROBLEMS. A. J. Blumenfeld*, A. G. Lossing. Department of Surgery, Wellesley Central Hospital, Faculty of Medicine, University of Toronto, Canada M4Y 1J3.

OBJECTIVE: To determine if a child population can solve medical problems. **DESIGN:** A pilot study of the problem solving abilities of children, aged 4 to 6 years. **SETTING:** The summer day camp program at Howard Public School, Etobicoke, Ontario. **SUBJECTS:** 15 children (6 boys, 9 girls) with a mean age at the time of testing of 5.1 years. 10 junior kindergartners, 3 senior kindergartners, and 2 first graders were present in our sample. **METHODS:** A medical problem with a known solution (determination of pulmonary wedge pressure by a Swan-Ganz catheter) was presented to all 15 children in the form of a children's story. The children were then asked to solve the problem by completing the story. **MAIN OUTCOME MEASURES:** Solutions given to the problem presented, and the subsequent interpretations of those solutions. A successful solution was regarded as one that utilized a flow-directed device, analagous to that of the Swan-Ganz catheter. **RESULTS:** Of the 15 children tested, 4 children were able to successfully solve the problem by using a flow-directed device. Other apparently non-practical, although extremely creative, solutions were suggested. **CONCLUSIONS:** By translating medical problems into simplistic children's stories, preschoolers can successfully give realistic and useful solutions.

ME2

ETHICAL DILEMMAS IN CLERKSHIP

D. Robertson*, ΨS. Ahmed, L. Hicks, Y. Lin, D. Robinson and S. Woodrow. Faculty of Medicine, University of Toronto. Ψ(authors in alphabetical order)

Background: The literature indicates that medical students encounter ethical dilemmas throughout their training. Anecdotal reports support this finding; yet very few medical schools have developed formal written policy to guide students facing ethical dilemmas. The Faculty of Medicine at the University of Toronto currently has no such written policy. **Objectives:** (1) To determine whether students in the Faculty of Medicine at the University of Toronto encounter ethical problems during clerkship. (2) To establish whether or not a formal written policy on ethics would be helpful for students. It is postulated that ethical issues exist in clerkship and that students would feel more comfortable in ethical situations if provided with a formal written policy. **Methods:** A survey instrument was designed addressing students' comfort level in ethically problematic situations, students' knowledge and opinions of currently available guiding resources, students' experience of ethical dilemmas and students' thoughts regarding the development of a formal policy on this topic. One hundred and twenty surveys were administered to third year students at the end of their final rotation in June 1997. **Results:** One hundred and eight surveys were returned (response rate = 90%). A majority of students (82%) felt uncomfortable when faced with an ethical dilemma. Only 53% knew where they would go for assistance. The most likely sources from which students would seek assistance were the rotation supervisor and resident/staff physician. Twelve percent of students had frequently witnessed unethical behaviour and twelve percent had frequently felt the pressure to act unethically. Eight-seven percent of students felt that a written policy dealing with ethical issues was required. **Conclusions:** Ethical dilemmas do exist in clerkship. The majority of students are unsure of the appropriate steps to take to resolve these ethical issues. Students were overwhelmingly in favour of the development of a formal written policy at the University of Toronto. Further research is required to explore the most ideal methods of policy development. In addition, this study highlights the need for more education, directed to both faculty and students, to assist students in dealing with ethical dilemmas.

ME3

A NEEDS ASSESSMENT OF SURGICAL RESIDENTS AS TEACHERS.

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Clinical clerks receive a significant proportion of teaching from residents. Residents, on the other hand, receive little formal training in teaching and learning, and resident teaching is inconsistently recognized and evaluated. The educational needs of surgical residents to function adequately in their teaching roles have yet to be ascertained. The purpose of this study is to determine the needs of surgical residents as teachers, and to begin establishing a teaching curriculum for the surgical residency. The needs assessment collected information from the three stakeholder groups: clerks, surgical residents and faculty. Issues were identified by clerk and resident focus groups, using the nominal group technique. This information was used to develop questionnaires for clerks and residents, and a semi-structured interview for selected faculty members. A triangulation of these three data sources was utilized to establish the needs of surgical residents as teachers. Preliminary results suggest agreement that: 1) teaching should be primarily the responsibility of the resident, and that residents' attitudes are significant, 2) feedback for residents is exceptionally important for improving their teaching, but is significantly lacking, 3) time management is a vital practical issue for residents as teachers, 4) residents are significantly unaware of clerks' formal surgical learning objectives, 5) active teaching methods are superior to passive. Similar suggestions were made by all sources as to the best techniques and locations to use for teaching. An important discrepancy was that residents indicated confidence in their role and effectiveness as teachers, and viewed this role with importance; clerks however indicated that residents were, on average, ineffective in addressing their individual teaching needs. This was particularly with regard to the use of certain teaching techniques. Another discrepancy was that while staff surgeons indicated that they felt the residents' role in teaching clerks was of utmost importance, residents did not perceive that the staff placed a high value on such teaching. This study has, from a multi-source perspective, assessed the needs of surgical residents as teachers and demonstrated the importance of initiating into the curriculum a protocol for teaching residents how to teach.

ME4

RESIDENCY SELECTION PROCESS AND PREDICTION OF RESIDENT PERFORMANCE: FRIGHTENING, ISN'T IT?

K. Mah-Poy*, N. Byrne, S.M. Shafir, D. Tannenbaum. Department of Family & Community Medicine, University of Toronto, Canada, M6J 3S3.

The process of selecting suitable, qualified candidates is an ongoing issue for residency programs. Because of the time, money and effort spent in resident selection, the selection process should be evaluated to determine its predictive validity. The aim of this study was to examine whether the residency selection process for Family Medicine at a Canadian university predicts resident performance assessed by program directors using a similar instrument to that used at entry. Entry data from the 1996-1997 first post-graduate year (PGY-1) matched through the Canadian Resident Matching Service (CaRMS), was collected. These data included the interview scores and file review scores. An instrument similar to the interview form was created and distributed to the program directors of each training site to evaluate the residents after completion of the PGY-1. There was a low positive, statistically non-significant correlation between the interview scores and the evaluation scores after completion of the PGY-1 ($r=0.1067$, $p=0.438$). Likewise, there was a low positive, statistically non-significant correlation between file review scores and the evaluation scores after the PGY-1 ($r=0.2298$, $p=.088$). It appears that the criteria examined at entry do not predict resident performance as assessed one year following entry into this residency program.

ME5

DEVELOPMENT OF A HAND-HELD COMPUTER HEMATOLOGY REFERENCE FOR HOUSESTAFF. J.P. Gladstone*, K.R.Imrie. Division of Medical Oncology/Hematology, Sunnybrook Health Science Centre, University of Toronto.

Pocket medical reference books are commonly used by housestaff but their educational value has never been formally assessed. We have developed and are currently evaluating a hand-held computer hematology reference. Hand-held computers can store and allow rapid access to large amounts of information. Our hypothesis is that access to such a tool will increase student comfort in managing hematology patients and may improve patient outcome. We conducted this project in 4 phases: a needs assessment, creation/assessment of a conventional paper reference, creation/evaluation of a computer version, and comparison of the paper and computer manuals. We present here the results of the first two phases of this project. A formal needs assessment was distributed to 20 housestaff. 95% indicated an interest in using a computer reference. A 60-page reference manual focusing on a practical approach to hematologic problems was prepared in accordance with the results of the needs assessment. Manuals were distributed to housestaff for evaluation with a questionnaire. The following domains were evaluated using a 5-point Richert scale: layout, content, and utility. 11/13 (85%) of questionnaires were returned. All felt that the manual was appropriate for their level of training and 90% indicated it was more useful than their current references. They felt that it was well laid out and easy to follow (4.5/5), and that the format was helpful (4.5/5). Fewer trainees felt that the manual would change how they would manage patients (3.7/5). Specific suggestions have been incorporated and we are currently translating the tool into a computer-based format for the Newton Message Pad 2000 (Apple corp. Cuprantino, CA) for comparison with the paper version. We hypothesize that the easy portability and rapid search capability may increase the proportion of trainees who feel that it will influence patient management.

Medical Genetics

MG1

THE ADULT PHENOTYPE OF VELO-CARDIO-FACIAL SYNDROME (VCFS).
E. Cohen*, S. Correia and A.S. Bassett. Schizophrenia Research Program, Queen Street Mental Health Centre, University of Toronto, Canada.

Velo-cardio-facial-syndrome (VCFS) is a multi-system genetic condition associated with an interstitial deletion on chromosome 22q11.2 that sometimes shows autosomal dominant transmission. The major features of VCFS, including learning disabilities, palatal ("velo") anomalies, cardiac anomalies, and minor facial dysmorphic features, have been described extensively in children. New evidence has accumulated connecting VCFS with adult-onset psychiatric disorders such as schizophrenia and bipolar illness. The adult phenotype of VCFS therefore needs to be delineated. All available clinical reports of VCFS in adults were reviewed and compared to published data on VCFS using a population of children. 76 adults with a mean age of 29.6 (SD = 7.4) were reported, of which 60 (78.9%) were ascertained through molecular investigations of affected offspring. The results indicate that most adults with VCFS tend to have fewer cardiac anomalies ($X^2 = 6.74$, df = 1, $p<.01$), but relatively similar rates of minor dysmorphic abnormalities, palatal anomalies and learning disability as children with VCFS. There were also more women than men among VCFS adults ($X^2 = 3.26$, df = 1, $p<.05$). Since the majority of adult patients were ascertained as parents of affected offspring, the results may reflect a bias involving reproductive fitness in women with a milder phenotype. Studies of adults identified independently of familial transmission will be necessary to clarify this issue and to further delineate an adult VCFS phenotype.

Clinical Finding	Goldberg et al (1993)	Literature Review
Sample Size	75	76
Mode of Ascertainment	craniofacial disorders clinic	variable
Learning Disability	99%	96% (52/54)
Cardiac Anomalies	82%	46% (31/68)
Palatal Anomalies	98%	87% (53/61)
Slender Fingers	63%	85% (17/20)
Ear Anomalies	70%	72% (18/25)
Gender	42 male/33 female	50 female/24 male

Medical Imaging

MI1

EVALUATION OF THE PRESURGICAL MR IMAGING PROTOCOL FOR PATIENTS WITH PRIMARY SPINDLE CELL SARCOMA OF BONE. M.J. Angel, J. Wunder, R.S. Bell, M. Blackstein & L.M. White. Musculoskeletal Oncology Unit, Mt. Sinai Hospital, University of Toronto, Canada.

Current preoperative management for patients with primary spindle cell sarcoma of bone (PSCSB) includes one magnetic resonance imaging study (MRI) obtained prior to chemotherapy (T1&T2-weighted axial and longitudinal images, i.e. standard imaging) and a similar second MRI obtained after chemotherapy. An evidence-based approach for MRI use in the preoperative management of these patients does not exist. Anecdotal evidence suggests that postchemo MRI in these cases is excessive since surgeons seem to plan surgery based predominantly on the prechemo MR sequences. **Hypothesis: The preoperative surgical planning for patients with PSCSB may be most efficiently performed on the basis of standard prechemo MR imaging, and a tailored postchemo MR study.** To test this, a retrospective study was performed to determine how the surgical plan changed following chemotherapy based on postchemo MRI, and to determine which postchemo MR sequences provided this information. Necessary information gleaned from the MR images which govern the orthopedic oncologist's surgical decision included: the tumour's intramedullary extent; articular involvement; dissectablility of neurovascular bundle, and extent of soft tissue involvement. Surgical decisions were either a variation of limb salvage or amputation. The orthopedic oncologist established a surgical plan independently, at separate sittings, based upon either the pre- or postchemo MR studies. Outlines were drawn on the images to indicate the location and extent of surgical resection. The extent of disease seen on the pre- and postchemo, preoperative MRI were compared for each patient as were the orthopedic oncologist's surgical plan. In 16/21 patients the surgical plan based on the postchemo MR sequences was identical to that obtained from the prechemo MRI. In the 5/21 surgical plans that did change, the new information was viewed best on axial and longitudinal T2-weighted images, i.e. the T1-weighted images were unecessary. In conclusion, preliminary evidence suggests that a tailored postchemo-preop MR study which includes axial & longitudinal T2-weighted images is sufficient for preoperative management of patients with PSCSB.

MI2

3-DIMENSIONAL FLOW-INDEPENDENT MAGNETIC RESONANCE ANGIOGRAPHY IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE. R. Ahmed*, G. Kim, J. A. Stainsby, J. K. Kim, N. Merchant, P. G. Kalman, G. A. Wright. Imaging Research, Faculty of Medicine, The Toronto Hospital and Sunnybrook Health Sciences Centre, University of Toronto, Canada, M4N 3M5.

We have demonstrated that arteries of the popliteal trifurcation in the leg can be imaged using 3-dimensional flow independent angiography (FIA), in both healthy volunteers and subjects who were previously diagnosed with peripheral vascular disease (PVD). These images have been compared with images obtained via 2-dimensional time-of-flight (2D-TOF) magnetic resonance angiography (MRA), 3-dimensional MRA with injection of a contrast agent, and x-ray conventional contrast digital subtraction angiography (DSA). 2D-TOF is a simple technique, but prone to image artifacts, while 3D MRA with contrast provides good isolation of arteries and is a rapid technique, with some challenges in set-up. FIA provides reasonable image resolution and signal-to-noise (SNR) ratios in under seven minutes, and results in good isolation of arteries from surrounding tissues in healthy volunteers and patients with intermittent claudication. FIA provides a clinically useful and noninvasive alternative to x-ray DSA in patients with PVD.

MI3

INTERNAL CAROTID ARTERY STENOSIS: EXPERIMENTAL AND PRELIMINARY CLINICAL EVALUATION OF THREE METHODS OF MAGNETIC RESONANCE ANGIOGRAPHY. A. Reid*, R.R. Farb, J.K. Kim, H.T.C. Nielsen, G.A. Wright. Department of Medical Imaging, Sunnybrook Health Science Centre, Faculty of Medicine, University of Toronto.

HYPOTHESIS: Magnetic Resonance Angiography (MRA) may obviate the need for intra-arterial digital subtraction angiography (IADSA) in the pre-operative assessment for carotid endarterectomy. PURPOSE: As part of an ongoing investigation into MRA for the purpose of non-invasively evaluating internal carotid artery (ICA) stenosis, the reliability of three methods of MRA was compared to the gold standard of IADSA. METHODS: This study consisted of two parts: a clinical study of 18 patients with symptomatic ICA stenosis; and an experimental study using a flow phantom with variable degrees of simulated stenoses (50% - 90%). The phantom study served to systematically evaluate the upper limit of each method of MRA in the depiction of stenosis. Both the patients and flow phantoms were imaged using two-dimensional time-of-flight (2DTOF), TWisted Radial Line trajectory (TWIRL) time-of-flight, gadolinium-enhanced MRA (GRAB) and IADSA. RESULTS: 2DTOF suffered from signal loss (signal gap) distal to the stenosis as a result of intravoxel dephasing. Consequently, the degree of stenosis was overestimated compared to IADSA. TWIRL was superior to 2DTOF in demonstrating the grade of stenosis. In the clinical study, the highest grade of stenosis depicted by TWIRL was 90%. However, there was a small signal gap in a case of TWIRL with 80% stenosis, as measured with IADSA. The GRAB patient results were somewhat more variable due to the problems encountered with accurate timing of the gadolinium injection relative to the initiation of the GRAB scan. However GRAB was the only MRA method which demonstrated the presence of an ulcer. In the phantom study, TWIRL depicted stenoses up to 90%, GRAB up to 70% and 2DTOF no greater than 50%. GRAB images defined the edges of the stenosis most clearly. CONCLUSION: TWIRL and GRAB are far superior to 2DTOF in evaluating carotid artery disease. Compared to IADSA, TWIRL is currently limited by blurred edges. GRAB is better able to depict edges than the other MRA methods and is the only technique which demonstrates ulcers. GRAB has the potential to depict stenosis > 70% with increased resolution in the A/P direction.

MI4

SEX AND MENTAL STATUS, NOT APOLIPOPROTEIN E, CORRELATE WITH PARIETAL TEMPORAL HYPOPERFUSION ON SPECT IN AD. Swartz, R., Black, S.E, Leibovitch,F., Caldwell,C., Ehrlich,L., St. George-Hyslop,P., Gladman,A., Szalai,JP. Cognitive Neurology, Sunnybrook H.S.C., University of Toronto, Canada, M4N 3M5.

Background: Previous functional imaging studies in Alheimer's Disease (AD) have usually had insufficient numbers for multivariate analyses of potentially relevant predictor variables. The e4 allele of Apolipoprotein E is a risk factor for the development of late-onset AD, but whether ApoE correlates with imaging measures in AD remains unsettled. **Design/Methods:** Sixty-three patients with possible/probable AD meeting NINCDS-ADRDA criteria from a university clinic underwent clinical and cognitive assessment. ApoE genotyping and SPECT. Scans were reconstructed and aligned to the AC-PC line and warped three-dimensionally to a SPECT atlas of 28 neuropsychologically normal, age-matched controls. Four lobar regions were defined by an automated cortical rim procedure and referenced to the cerebellum. Age at onset, duration of disease, sex, education, ApoE status, and Folstein MMSE score were entered into stepwise regression analyses predicting perfusion ratios in the frontal, temporal and medial occipital regions. **Results:** In this sample of 24 women and 39 men, mean age of onset was 67 +/- 10, duration was 4 +/- 2 years, years of education was 14 +/- 4, and mean MMSE score was 21 +/- 5 (range 4-29). An e4 allele was present in 67% of men and 46% of women. Lower MMSE scores and male sex significantly predicted lower temporal and parietal perfusion (R^2=25%, $p<0.001$). Longer duration predicted occipital hypoperfusion, accounting for 11% of the model variance ($p<0.01$). No other variables emerged as significant in any analysis. **Conclusion:** Sex and cognitive impairment as indexed by the MMSE were significant predictors of temporal and parietal hypoperfusion in AD patients. Overall, women had less parietal and temporal hypoperfusion, compared to men for a given level of cognitive impairment. This finding is consistent with our previous MRI study, in which women had less parietal and temporal atrophy. The presence of ApoE e4 did not significantly predict regional cerebral blood flow. The study demonstrates the importance of multivariate analysis to account for the simultaneous effects of potentially relevant predictor variables and to avoid simplistic conclusions about their relationship to functional imaging parameters in AD.

MI5

PRESYNAPTIC AND POSTSYNAPTIC SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY (SPECT) CAN BE USED TOGETHER IN THE DIAGNOSIS OF PARKINSON'S DISEASE(PD). S. S. Erami*, M. Ichise. Department of Nuclear Medicine, Mount Sinai Hospital, Toronto, M5G 1X5.

Methods and results: Using the cocaine analogue, $C^{123}IT$, as a gamma-emitting radiotracer for presynaptic dopamine transporters, we have confirmed that PD patients have a population of dopaminergic presynaptic transporters that is diminished in the striatum; particularly in the putamen and less so in the caudate. On the other hand, using ^{123}IBF, a gamma-emitting postsynaptic binder of dopamine receptors, we have shown that these receptors are normal or slightly increased in number in PD as an adaptation to the decreasing dopamine.

Discussion: The results above enable one to diagnose PD on the basis of an affected putamen in the CIT scan and a normal or upregulated IBF scan. They can also distinguish other modes of parkinsonism such as corticobasal degeneration, multiple system atrophy, and progressive supranuclear palsy. This is possible because in these conditions, the IBF scan is decreased, as well as the CIT scan which is uniformly decreased in the striatum and not just in the putamen as with PD. The differentiation of PD from these other related disorders is very important as they have prognoses and treatments that are very different than PD's. Post mortem studies have shown the clinical diagnosis of PD to be wrong in 20% of cases. The ability of SPECT to visualize the brain is revolutionary with great promise in the correct diagnosis and treatment of the parkinsonian syndrome.

Neuroscience

NS1

ENHANCEMENT AND CANCELLATION OF THE INITIAL VESTIBULO-OCULAR REFLEX DURING RAPID ACTIVE AND PASSIVE HEAD-ON-BODY ROTATIONS. A. Tsiaprailis, J.A. Sharpe. Division of Neurology, The Toronto Hospital, University of Toronto, Canada.

The vestibulo-ocular reflex (VOR) stabilises retinal images during head movements by generating smooth eye movements in the opposite direction at short latency. VOR gain is eye velocity divided by head velocity. Ideal VOR gain is 1.0 for a distant target. The VOR can be modified by vision in low velocity head movements, resulting in its enhancement or cancellation. In addition, non-visual cues might also be expected to modify the initial VOR (iVOR), by altering the gain of the reflex. In a head-on-body movement, such cues may arise from a cervico-ocular loop that may be potentiated with active movement. This study determines whether the iVOR gain or latency differed between rapid active and passive head-on-body movements or "impulses" (AI and PI, respectively). Eye and head movements were recorded in ten subjects who underwent both types of impulses under dark conditions, light conditions (for VOR enhancement), and with a target coupled to the head (for VOR cancellation). The first 65 msec of the reflex were measured. There were no significant differences ($p<0.05$) in iVOR gain or latency, between active and passive group means under all three conditions but some individual subject means differed between groups. Comparing PI to AI, iVOR gains significantly decreased in 4 subjects under dark conditions, and 2 subjects in light. However, iVOR gain increased in 1 subject under dark conditions, and 2 subjects in light. In addition, longer latencies were seen with PI, both in light and dark. iVOR enhancement occurred in only 2 subjects undergoing PI, while decreasing in 2 others undergoing PI, and in 2 performing AI. iVOR cancellation occurred in all subjects undergoing AI and 3 of 4 subjects undergoing PI. In conclusion, visual cancellation of the iVOR can occur in rapid head-on-body rotations. However, visual iVOR enhancement is not evident in most individuals. Finally, it appears that potentiation of the cervico-ocular loop, in active impulses, decreases the iVOR gain in some individuals.

NS2

PYRAMIDAL NEURON DEVELOPMENT IN CAT VISUAL CORTEX FOLLOWING NORMAL OR MONOCULAR VISUAL EXPERIENCE. Victor D. Pegado*, Michael J. Eckert, and Kathryn M. Murphy. Department of Psychology, McMaster University, Hamilton, ON.

The monocular antibody SMI-32 labels a subset of pyramidal neurons that express a high molecular weight subunit of neurofilament protein. In adult mammalian visual cortex neurons expressing neurofilament-H are found in layers II/III, V, and VI. We examined the laminar development of SMI-32 immunoreactivity in the visual cortex of the kitten and the effect of monocular deprivation upon the pattern of labeled pyramidal neurons. SMI-32 label was apparent in neurons in layer V at the earliest age studied and reached mature levels by 3-4 weeks of age. Neurons in both layers II/III and layer VI did not begin to express neurofilament-H until 3-4 weeks of age and then slowly matured to adult levels. Thus, the laminar pattern of expression does not follow the typical inside-out development sequence since layer VI develops much slower than expected. Following monocular deprivation, the pattern of SMI-32 immunoreactivity in layer VI was notably patchy. The expression of SMI-32 in layer VI is therefore influenced by visual experience showing that the development of layer VI is dependent upon the pattern of retinally-driven activity.

NS3

Changes in Kv 1.4 Potassium Channel Protein and mRNA Expression After Chronic Spinal Cord Injury.

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Conduction failure of surviving axons in the subpial rim after chronic spinal cord injury (SCI) appears to contribute to paralysis. These axons show disruption of the myelin sheath and abnormal activation of kinetically 'fast' K^+ channels. To date, the characterization of these K^+ channel α subunit proteins in relation to injury has not been investigated. In this study, we used molecular techniques to investigate the distribution of one member of the Shaker subfamily of K^+ channel proteins, Kv 1.4, and its genetic expression in normal and chronically injured spinal cord.

Injury was performed on adult Wistar rats by compressing the spinal cord at T7-T8 with a modified aneurysm clip (closing force of 23g) for 1 minute. Animals were sacrificed 6 weeks after SCI. Levels of Kv 1.4 protein were investigated by Western blotting and immunocytochemistry. Changes in Kv 1.4 mRNA were examined using RNase Protection Assay and RT-PCR.

Western blots showed an increase in Kv 1.4 protein in the dorsal column of chronically injured cords when compared to normal cord. Immunocytochemical staining for Kv 1.4 was also increased at the injury site. RNase Protection Assay and RT-PCR showed an increase in Kv 1.4 mRNA in injured spinal cords, as well as in the midbrain encompassing the red nucleus, and dorsal root ganglia of injured animals.

This study shows that increases in Kv 1.4 K^+ channel protein found in chronic SCI are facilitated by an upregulation of Kv 1.4 gene expression. This upregulation and altered distribution of Kv 1.4 K^+ channel protein following chronic SCI may contribute to axonal dysfunction. Therefore therapeutic strategies targeting K^+ channel proteins or gene expression may improve neurological function in paralyzed patients.

NS4

A BIOCHEMICAL TEST FOR MULTIPLE SCLEROSIS BASED ON CHARGE MICROHETEROGENEITY OF MYELIN BASIC PROTEIN. J.M. Burton* and M.A. Moscarello. Department of Biochemistry Research, The Hospital for Sick Children, University of Toronto, Canada, M5G 1X8.

Multiple Sclerosis (MS), considered an autoimmune disease mediated by T-cell response to host oligodendrocyte myelin proteins, is the most common neurological disease in young and middle-aged adults in Canada. The purpose of this project was to develop a diagnostic biochemical assay for MS that was sensitive, specific, and could be used in diagnosis and treatment monitoring. This assay, which employs cerebrospinal fluid (CSF), is based upon the known charge microheterogeneity of Myelin Basic Protein (MBP), a component of myelin. Previous research has shown that unfractionated MBP, which has six charge isomers that differ from one another by a relative charge of 1+, can be separated into these charge components by alkaline-urea gel electrophoresis. When run with ^{125}I-labelled MBP, the bands corresponding to the various components can be seen by autoradiography. To determine the ratio of the least positive isomer (C-8) to the most positive one (C-1), the radioactivity in each band can be measured. An elevated ratio obtained with MBP from autopsy brain is correlated with demyelination and MS clinical severity. Our hypothesis was that human CSF, which can contain trace amounts of MBP in MS, could be used to determine C-8/C-1 ratios after radioiodination. In CSF trials, the CSF, which was lyophilized and reconstituted in H_20, and ^{125}I-labelled CSF containing 30,000 cpm were added to the gel in 4M urea. These samples were run for 8 hours at reversed polarity, stained with Amido black and destained to identify the position of the markers, and then exposed to X-ray film at -70°C for approximately 72 hours. Western blotting of CSF samples, run on an alkaline-urea gel, using specific MBP antibodies was also done as an alternate non-radioactive method. We were unable to detect MBP on the gel or film by either method. Although too early to make definitive conclusions, the amount of MBP in CSF may be too dilute, or the presence of salts and other substances may interfere with the migration in the gel. It may still be possible to use CSF in this assay, but it will require the removal of these materials and further processing.

NS5

FRONTOTEMPORAL DEMENTIA: A NEUROPATHOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY. S.M. Laval*, B. Young, L.C. Ang. Division of Pathology, Sunnybrook Health Science Centre, University of Toronto, E419-2075 Bayview Avenue, North York, ON, Canada, M4N 3M5

Fronto-temporal dementia is not a distinct group of diseases. It is a clinical syndrome which includes: frontal lobe degeneration, Pick's disease, motor neuron disease with dementia and primary progressive language disorder. In the past as a group they have been largely overlooked as a cause of dementia. Those with Pick bodies were identified as Pick's disease and those without Pick bodies were called Pick's disease without Pick bodies. This later group has also been called dementia with no distinct histopathological features. Fronto-temporal dementia has been overlooked as other dementia such as Alzheimer's and Pick's have been more extensively examined. These diseases are still poorly understood and may not be a group but involve the frontal lobe with no other distinct histological changes. For this reason we reviewed the neuropathological findings of autopsy cases from Sunnybrook from 1980 to 1997. From there we selected 40 cases for histological examination out of which 22 were included in this study The areas examined included the frontal lobe, hippocampus, amygdala, temporal lobe, inferior parietal lobule, orbital lobe, cingulate gyrus, temporal gyrus, and frontal gyrus. Cases of Alzheimer, multi-infarct dementia, Creutzfeldt-Jacob disease, progressive supra-nuclear palsy, and cortical basal ganglionic degeneration were excluded. The cases of Pick's disease, and frontal temporal degeneration with or without ALS were examined. In all of the cases gliosis, spongiosis, and neuronal loss were found in the frontal and/or temporal lobe. Immunohistochemical studies were performed using tau, ubiquitin and alpha beta crystalin staining. Ubiquitin stain showed swollen neuritic processes in three cases, otherwise the stains showed no distinct features apart from Pick bodies. A comparison was made of the different subgroups of this disease.

Obstetrics and Gynecology

OB1

THE USE OF TOCOLYTICS FOR THE TREATMENT OF PRETERM LABOR: A SYSTEMATIC REVIEW OF THE LITERATURE. K.Gyetvai*, M.E. Hannah, E.D. Hodnett, A. Ohlsson Departments of Obstetrics and Gynaecology, Paedriatrics, Women's College Hospital, Faculty of Nursing and the University of Toronto Maternal and Infant Reproductive Health Research Unit at the Centre for Research in Women's Health, University of Toronto, Canada

The objective of this review was to examine the effectiveness of any tocolytic when compared to a placebo or no tocolytic for preterm labor.

Data Sources: Both MEDLINE (1966 - 1997) and the Cochrane Controlled Trials Register were searched using the key words randomized controlled trial, preterm labor, tocolysis, betamimetics, ritodrine, terbutaline, hexaprenaline, isoxuprine, prostaglandin synthetase inhibitors, indomethacin, sulindac, calcium channel blockers, nifedipine, oxytocin receptor blockers, atosiban, nitroglyceride and magnesium sulfate. A hand search of 6 relevant journals was also undertaken to obtain articles published between January and March of 1997.

Methods of Study Selection:. Twelve articles met the entry criteria. To be included in the review, articles had to be randomized controlled trials, comparing a tocolytic to a placebo or no tocolytic which reported on perinatal or maternal outcomes. Women enrolled in the studies had to be between 20 and 37 weeks gestation and present with uterine contractions with or without cervical dilatation or effacement. Studies were excluded if loss to follow up was ≥ 20% of those originally enrolled, if ≥ 20% of patients in any one randomized group received a tocolytic in addition to the drug being studied or if data were not reported on a per patient basis.

Results: Articles were reviewed and data were abstracted independently by two of the authors. Discrepancies were resolved by consensus. Data were combined for all trials and for those evaluating specific types of tocolytic therapy. A typical odds ratio with a 95% confidence interval was calculated and recorded for each outcome. Tocolytics were found to prolong pregnancy but this was not associated with a substantial increase in gestational age at birth, or improved perinatal outcomes. Women receiving tocolytics experienced an increase in adverse side effects.

Conclusions: There is no indication that tocolytics improve the outcome for women experiencing preterm labor.

OB2

INTRAPARTUM EVENTS ASSOCIATED WITH RATES OF FULL, PARTIAL, TOKEN, AND NON- BREASTFEEDING. T. Levine*, J. Watson-MacDonell, S. Halpern, D. Wilson. Department of Anesthesia, and Faculty of Nursing, Women's College Hospital, University of Toronto, Canada, M5S 1B2.

This observational study examines whether events and interventions during labour and delivery are correlated with rates of breastfeeding at six weeks post-partum. After REB approval, the charts of women delivering at Women's College Hospital over a six week period were reviewed. Inclusion criteria included low risk pregnancies, and women who were planning to breastfeed. Information collected by chart review regarding intrapartum events and interventions included length of labour, presentation, mode of delivery, suctioning, APGAR scores, analgesics and anesthetics, and other drugs (antibiotics, gravol). The primary outcome variable was the degree of breastfeeding at six weeks post-partum and was collected by standardized telephone interviews. Full breastfeeding is defined as feeding breast milk with no other caloric supplements, or caloric supplements given less than daily. Partial breastfeeding is breastfeeding with caloric supplements given daily, or more than daily. When the frequency of feeding breast milk becomes less than daily, breastfeeding degree is defined as token. The final sample size included 189 women. At six weeks post-partum 70% were fully breastfeeding, 20% were partially breastfeeding, 2% were token breastfeeding, and 8% were no longer breastfeeding. Logistic regression and correlation analyses were performed with a P value equal to 0.05 and no statistically significant relationships were found between intrapartum events and interventions and breastfeeding rates at six weeks post-partum. Breastfeeding success is multifactorial and does not appear to be correlated with intrapartum events or interventions in this population.

OB3

DEXAMETHASONE LEVELS IN FETAL CORD AND MATERNAL BLOOD AFTER PRENATAL DEXAMETHASONE ADMINISTRATION IN SINGLE AND MULTIPLE PREGNANCIES. E. Ola*, E. Quist-Therson, K. Amankwah, A. Ohlsson. Department of Obstetrics and Gynaecology, Women's College Hospital, University of Toronto, Canada, M5S 1B2

The effectiveness of antenatal steroids in preventing respiratory distress syndrome in twin gestations is not yet established. A subanalysis of twins in the NIH Collaborative Trial suggested that levels of dexamethasone in twins were very low and that the level in twin B was half that in twin A. **Hypothesis:** On the basis of these findings, we suggest that dexamethasone levels in twin pregnancies do not reach sufficient levels to activate the glucocorticoid receptor and this might explain the clinically observed differences in the effectiveness of antenatal steroids in twins and singletons. **Objective:** To measure dexamethasone levels in twins and singletons after prenatal administration and determine if significant differences exist. **Methods:** Expectant mothers between 24 and 40 weeks gestation were recruited into a study previously approved by Women's College Ethics Committee. 6 mg of dexamethasone was given intravenously prior to delivery. Blood samples were collected from the mother and from the infant's umbilical cord shortly after delivery. A radioimmune assay for dexamethasone was performed on each sample using a previously validated method. **Results:** 8 patients with singleton pregnancies and 7 with multiple pregnancies were recruited yielding a total of 38 samples for assay. Dexamethasone levels in the patients with multiple infants was not lower at any time studied compared to the singletons. Dexamethasone levels in the infants mirrored those in the mothers with higher levels in the multiple infants until about 70 min. At this point, levels equalized and subsequently fell below those of the singletons. There were no differences in dexamethasone levels between twin A and twin B at any time ($p=0.98$). **Conclusions:** Our findings do not support the hypothesis that peak levels in twin pregnancies are lower than in singletons. No differences in levels were seen between twin A and B and that cannot explain the observed clinical differences in twins. We speculate that levels of free dexamethasone in multiple mothers are higher because of lower albumin levels and less binding. Consequently, more free drug crosses the placenta to the babies. The steeper fall off in dexamethasone levels in twins may be reflective of the dual fetal metabolism of the drug once it crosses the placenta.

OB4

MAINTENANCE OF AN INTACT PROGESTERONE RECEPTOR SYSTEM IN THE HUMAN LOWER UTERINE SEGMENT IS CONSISTENT WITH RELAXATION IN THIS REGION DURING LABOUR.

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Progesterone (P) is essential for the maintenance of pregnancy in part due to its inhibition of uterine contractility. In most species this inhibitory action is terminated by decreased P production. In humans however, there is no evidence of any such decrease, suggesting that P dominance over the myometrium must be overcome by a mechanism other than P withdrawal. The signalling pathway through which P acts includes its receptor (A and B isoforms), as well as a series of receptor-associated chaperone and co-activator proteins. A change in any of these components could elicit a functional withdrawal of P. Myometrial tissue was therefore collected from the lower uterine segment of labouring and non-labouring women during cesarian section deliveries. We first investigated whether labour was associated with a decrease in P receptor expression (mRNA and protein), or a change in the relative amounts of the A and B receptor isoforms. These isoforms exhibit different binding affinities and transcriptional activities and a change in their ratio in other tissues has been shown to alter P action. No significant changes were found in either the total levels of the P receptor ($p>0.01$) or the relative expression of the A and B receptor isoforms ($p>0.01$). We then addressed the possibility that a change in expression of heat-shock proteins (HSP) might invoke a functional P withdrawal since these "molecular-chaperones", maintain activation/inactivation of these receptors. We identified the expression of mRNA encoding three HSPs (HSP-90α, HSP-90β, and HSP-70) in the human myometrium. We did not find a change with the onset of labour, but did find an increase in HSP expression in sheep myometrium during labour ($p<0.01$, as previously shown by Wu et al. Endoc. 1996; 173:5685). It is possible that P withdrawal is not required for human labour, or that other components of the P signalling system are altered. We have previously observed that human labour is associated with an increased expression in the lower uterine segment of genes related to inhibition rather than stimulation of contractility. We thus suggest that there is no P withdrawal in this region of the uterus, and speculate that functional P withdrawal only occurs in the fundal region.

Oncology

ON1

BREAST CANCER IN WOMEN FOLLOWING SUPRADIAPHRAGMATIC IRRADIATION FOR HODGKIN'S DISEASE

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Purpose The relative risk (RR) of breast cancer (BC) in women following supradiaphragmatic irradiation of Hodgkin's disease (HD) has been reported to be elevated. This is especially true in younger women. A retrospective chart review was conducted to investigate the incidence of BC and to describe the characteristics of these cases. Based on these results, predictions are made regarding the future number of breast cancers in this population and plans for surveillance are outlined.

Patients and Methods A chart review was conducted at the Princess Margaret Hospital from 1965 through 1990 to include women 30 years old or less at the time of supradiaphragmatic irradiation for HD.

Results Of the 427 women with a mean follow-up of 12.3 years, 15 women subsequently developed BC. The median age of BC diagnosis was 41 years (30-52) and the median interval from irradiation was 17 years (9-25). Laterality was equally divided and 50% of the tumours were located in the inner quadrant ("in-field" areas) of the breast. Two women developed bilateral metachronous tumours. The RR of BC in this cohort is 10.3 (95% CI: 5.8, 17). It is predicted that in our patient population there will be a total of 22, 33, and 42 cases of BC by the years 2000, 2005, and 2010, respectively.

Conclusion Compared to women in the general population, young women irradiated for HD have a 10-fold higher risk of developing BC. In this specific group of women, we can predict the number of cases of BC we expect to see in the forthcoming years. It is hoped that improved surveillance will allow early detection, timely treatment, and improved progress for these at-risk women.

ON2

CHARACTERIZING THE MOLECULAR MECHANISMS OF LOVASTATIN-INDUCED APOPTOSIS.

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Recently, Lovastatin, a non-reversible HMG-CoA reductase inhibitor has been shown to induce apoptosis in a cell-type specific manner. In response to lovastatin treatment, acute myeloid leukemia (AML) cells were found to undergo massive apoptosis whereas acute lymphoblastic leukemia (ALL) cells were resistant. While this specificity highlights the potential use of lovastatin in the treatment of specific malignancies, its use cannot be appreciated without a better understanding of its mechanism of action. Therefore, the purpose of this study was to characterize some of the molecular players involved in the lovastatin-induced apoptosis pathway. First, endogenous expression levels of some genes involved in apoptosis, namely *bcl-2*, *bax*, *mdr-1* and *HMG-CoA* reductase were determined in ALL and AML cells by northern and western blot analyses. Results showed no correlation between P-gp expression and apoptosis. The HMG-CoA reductase levels were found to be induced in both ALL and AML cell lines in response to lovastatin. Interestingly, bcl-2 levels were found to decrease in lovastatin-treated AMLs but not in lovastatin-treated ALL cells. Finally, *bax* levels were found to be highly expressed in both subsets of cells. Second, to determine whether lovastatin sensitivity could be directly modulated, *bcl-2* was introduced in AML-5 cells by retroviral infection and Bcl-2 protein expression confirmed by western blot analysis. Apoptosis sensitivity to lovastatin was reassayed by MTT. AML-5 cells expressing ectopic Bcl-2 (AML-5/Bcl-2) were found to be resistant to lovastatin-induced apoptosis indicating that overexpression of Bcl-2 can modulate lovastatin sensitivity. Furthermore, the role of GSH (reduced glutathione), mitochondrial membrane permeability (MMP) and reactive oxygen intermediates (ROI) in the mechanism of lovastatin induced apoptosis was determined by flow cytometry analysis. Results showed no ROI production in either lovastatin-treated AML-5 or AML-5/Bcl-2 cells. Interestingly, a decrease in GSH and MMP was observed only in AML-5 cells undergoing apoptosis but not in AML-5/ Bcl-2 resistant cells. Finally, since lovastatin has well defined pharmacokinetics, it was offered to four selected patients at the OCI leukemia clinic as a potential anti-cancer drug. Results are promising. One patient in particular showed a significant and sustained decrease in WBCs count. In summary, we have started to delineate some of the molecular and biochemical effectors of lovastatin-induced apoptosis. More importantly, our study has emphasized the role of lovastatin as a potentially new cancer drug.

ON3

OXIDATIVE STRESS OF 2-NITROIMIDAZOLES AS A MECHANISM FOR PERIPHERAL SENSORY NEUROPATHY.

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The 2-nitroimidazole class of compounds has been used clinically as an adjunct to radiotherapy to sensitize resistant hypoxic regions in solid tumours. During these clinical trials, patients experienced a dose-limiting peripheral sensory neuropathy, which limited the therapeutic effectiveness of these compounds. A possible role of oxidative stress in the aerobic cytotoxicity of 2-nitroimidazoles was investigated by using a model compound, 1-methyl-2-nitroimidazole (INO_2). The sensory neuronal cell line ND7, a hybrid of rat neuroblastoma and mouse primary sensory neurons, was used to test the hypothesis that INO_2 aerobic exposure leads to cytotoxicity via an oxidative mechanism. The ND7 cells were continuously exposed to therapeutic doses of INO_2 (0.01 mM, 0.05 mM, 0.1 mM, 0.5 mM, 1 mM, 2 mM, and 5 mM) for 24, 48 and 72 hours under aerobic conditions. Cell viability, reactive oxygen intermediates (ROIs), antioxidant intracellular glutathione (GSH) and the mitochondrial membrane potential (MMP) were assayed following continuous INO_2 aerobic exposure. Data showed that the ND7 neuronal cells were more sensitive to aerobic treatment at 5 mM than other rodent cell lines (Chinese hamster ovary cells and rat embryo fibroblasts) previously tested. A 2 to 6 fold increase in the fluorescent dye rhodamine-123 was observed at 72 hours following all INO_2 concentrations tested, suggesting the generation of ROIs. Furthermore, GSH levels were decreased to 25% of control following 5 mM INO_2 aerobic treatment at 48 hours. A decrease of 40% and 50% in the MMP was observed at 72 hours continuous exposure at both 2 mM and 5 mM INO_2, respectively. This suggests that the kinetics of INO_2 aerobic cytotoxicity resulted initially from GSH depletion, followed by loss of mitochondrial activity, ROI generation, and finally cell death. Studying the cellular effects of INO_2 on a neuronal cell line, allows for further insight into trying to understand the biochemical mechanism involved in the peripheral sensory neuropathy that was observed during clinical trials of 2-nitroimidazoles. Therefore, an understanding of the mechanism involved in the aerobic cytotoxicity of INO_2 may result in better design of new compounds and/or interventions that will reduce the effect of oxidative stress, thereby decreasing normal neuronal tissue toxicity and increasing therapeutic efficacy.

Ophthalmology

OP1

VISUAL ACUITY AND REFRACTIVE RESULTS OF 122 CONSECUTIVE PHOTOREFRACTIVE KERATECTOMY PROCEDURES FOR MYOPIA.

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Department of Ophthalmology, Faculty of Medicine, Toronto Hospital, University of Toronto.

Methods. We reviewed the results of the first 122 consecutive excimer laser photorefractive keratectomy procedures (70 patients) by two surgeons at one center from February 1997 to August 1997. Follow up was obtained at 1 week (80%), 1 month (82.7%), and 3 months (63.2%).
Outcome Measures. Included post operative uncorrected visual acuity, spherical and cylindrical equivalents, complications (haze, edema, and epithelial irregularity), percentage of patients placed on topical steroids and those requiring retreatment.
Results. A mean preoperative myopia of -3.2 (SD 1.6) dioptres (D) {Range -0.5 to -7.0} decreased to -0.21 (SD 0.54) D {Range -1.75 to +1.25} at 3 months follow up. A mean astigmatism of -0.82 (SD .69) D {Range 0.25 to -3.75} decreased to -0.28 (SD 0.37) D {Range -1.5 to +0.75} at 3 months follow up. Postoperative uncorrected visual acuity for eyes not monovision targeted at 3 months was 20/40 or better for 100% of low myopes (0 to -3 D), 94% for moderate myopes (-3 to -6 D), and 100% for high myopes (-6 to -7.5 D). The difference between achieved and targeted refraction (including monovision eyes) at 3 months follow-up was -0.14 (SD .42) D {Range -1.25 to +0.75} for low myopes: +0.31 (SD .55) D {Range -0.75 to 1.75} for moderate myopes; and +0.58 (SD .59) D {Range -.25 to 1.75} for high myopes. No vision threatening complications occured. Results are in accordance with previous studies on PRK outcomes.

Patient Education

PE1

MEDICATION EDUCATION OF ACUTELY HOSPITALIZED ELDERLY PATIENTS. R.K. Han*, S.M.H. Alibhai, G. Naglie. Department of Medicine, The Toronto Hospital, Division of Geriatric Medicine, University of Toronto, Canada.

Objectives: To determine the amount of time spent providing medication education to elderly patients, its impact on patients' level of knowledge and satisfaction, and the barriers to providing medication education.

Design: Telephone survey of patients, and interviewer-administered survey of physicians and pharmacists.

Setting: General medical wards in a tertiary care teaching hospital.

Participants: Patients over 65 years of age regularly taking at least one medication.

Main Outcome Measures: Patient demographics, medication use, time spent receiving/providing medication education, and satisfaction scores.

Results: Sixteen patients with a mean age of 74.9 were surveyed. They reported that physicians spent a mean of 12.8 minutes (range 0-60) and pharmacists spent a mean of 7.8 minutes (range 0-40) providing medication education. Eight patients (50%) reported receiving no education from either physician or pharmacist. Patients who received education were prescribed a mean of 2.0 new medications (range 0-4) compared to a mean of 0.6 (range 0-2) for patients without education. Both groups of patients made many medication errors, but patients who received education reported higher satisfaction scores. Physicians identified lack of time as the main barrier to providing education, while pharmacists cited lack of notification of discharge plans as the main barrier.

Conclusions: Fifty percent of elderly patients reported receiving no medical education. Elderly patients with and without medication education from physicians and pharmacists made a large number of medication errors. This suggests that further effort is required to educate elderly patients sufficiently to reduce their medication errors.

PE2

LEARNING NEEDS OF LIVER TRANSPLANT PATIENTS AND THEIR SUPPORT PEOPLE. J. Yoo,* S. Abbey, R. Cashmore, P. Greig. Liver Transplant Program, the Toronto Hospital, University of Toronto, Canada, M5G 1X8.

Learning needs and barriers to leaning have been studies on 92 liver transplant patients and their families
Method. The study involved a cross-sectional design with a mailed questionnaire and informed cousent information and consent form sent to all patients and their support persons on the liver transplant waiting list in Feb. 1997 as well as to 6 to 8 months post liver transplant recipients and their support persons
Results: The most useful source of information that all 4 groups identified were: their transplant physicians, transplant coordinators, and the transplant patient manual. The Health Locus of Control scale did not differentiate learning needs or recommendations they would make to new transplant candidates. Comparing transplant recipients and candidates, the notable findings were on the quality of life measure showing a significant improvement of quality of life across all domains. The support people did not show an improvement in their quality of life once the patient they were supporting was transplanted. They continued to experience quite significant disruption related to the illness and treatment of the individual that they were supporting. More detailed analysis is presently being done and will be reported on.
Conclusion Patients and support people recognize the importance of education to prepare them for liver transplantation. They identify the importance of speaking with team members including the transplant physicians and coordinators and the use of a variety of different resources

PE3

AN EVALUATION OF PATIENT EDUCATION AND COLORECTAL CANCER. Cara B. Betel*, Marlene Greenberg, and Pamela Chart. Preventive Oncology Program, Toronto-Sunnybrook Regional Cancer Centre, Faculty of Medicine, University of Toronto, Canada, M4N 3M5.

Colorectal cancer is a prevalent and potentially fatal disease. It is the third most common form of malignant tumour and third most common cause of death due to cancer in North America. Despite its health burden, very little information about the disease is presented to the public. The resultant information gaps about the disease create further health problems and social difficulties. The goal of this project was to determine where these information gaps exist, and to design and produce a strategy of filling them. Based on a needs assessment conducted previously, a seminar format with a question period was selected. Two populations of individuals were targeted - those at an increased risk of colorectal cancer and those who had been previously diagnosed with the disease. Seminars for each of these two populations were prepared, and each reflected the informational gaps of these populations. The seminars were evaluated by a pre- and post-seminar test and a questionnaire. Results indicate that the seminar is a powerful public education tool, which may affect the future health of the population serviced. The seminars were successful and should be repeated on a yearly basis.

Psychiatry

PS1

THE MEASUREMENT OF AFFECTIVE LABILITY IN A CLINICAL SETTING: A COMPARISON BETWEEN THE AFFECTIVE LABILITY SCALE (ALS) AND THE VISUAL ANALOGUE MOOD SCALE (VAMS). J. Villella*, Dr. P. Links, Dr. R. Heslegrave. **Dept. of Psychiatry, Wellesley Hospital, University of Toronto, M4Y 1J3.**

Affective lability is a personality trait characterized by frequent, dramatic, and relatively short-lasting mood swings within a 24-hour period. Because of its inclusion as a criterion for the diagnoses of a variety of psychiatric disorders (e.g., Borderline Personality Disorder), a practical and accurate way of measuring affective lability would help make such diagnoses more consistent and valid. While the use of VAMS is the most direct (and widely accepted) method to specifically measure this trait, repeated daily measurements of mood over 1-2 weeks is difficult to implement in a clinical setting and results in high rates of patient non-compliance with the procedure. The purpose of this research was to determine if a faster and more convenient instrument, namely the ALS, could yield results as reliable as the VAMS procedure. A group of 11 psychiatric inpatients were studied over a 2-week period in an inpatient psychiatric facility. Patients completed the ALS scale twice, when they were first admitted to the facility and stabilized and at the end of the 2 weeks. In addition, patients were asked to complete a VAMS measuring their mood in the morning and evening on each of the 14 days. It was hypothesized that the ALS would be significantly correlated to daily variation on their mood. To examine the hypothesis, the scores on the ALS scale (at 1 and 14 days) were correlated with the standard deviation in the VAMS scores. The results showed that the ALS score at admission was not significantly correlated with the variation in mood over the 2 weeks but the ALS score on day 14 was highly correlated with the variation over the previous 2 weeks (r=.74, p=.01). On the other hand, the ALS score at admission was significantly correlated (r=.69, p=.02) with the degree of positive mood over the following 2 weeks. To examine the effects of treatment, the same relationships were examined for each week independently. This analysis yielded identical results in that the ALS score at admission was significantly related to the level of mood during weeks 1 and 2 while the ALS score after 14 days was related to the variation in mood over weeks 1 and 2. These data suggest that the ALS at the point of admission reflects the level of positive mood whereas following the persistent reflection on their variation in mood, the ALS score correlates highly with that variation in mood. While the ALS is highly related to mood level and variation, it would appear that the ALS only reflects lability if patients attend to their mood variation for an extended period.

Public Health

PH1

EVALUATION OF HEPATITIS B SURVEILLANCE SYSTEM IN 4 PUBLIC HEALTH UNITS. E.M. Prosen*, I.L. Johnson. North York Public Health Department, North York, Ontario, M2N 5V7.

Following an outbreak of hepatitis B among EEG clinics in Metro Toronto, a study was conducted to determine the sensitivity of disease reporting. This was accomplished by comparing the results of active and passive surveillance systems used during the outbreak investigation. Through reviews of the original data reports and personal interviews of health unit staff, it was determined that 57% of hepatitis B cases were correctly reported. This sensitivity varied among the 4 health units in the study from a low of 20% to a high of 85%. Based on this study, recommendations for improving the public health surveillance systems have been made.

Respiratory Medicine

RE1

ADENOVIRAL-MEDIATED INTERLEUKIN-10 GENE TRANSFECTION: OPTIMAL DOSING IN A RAT MODEL. I.D. Bookman*, S. Cassivi, A. Boehler, M. Liu, S. Keshavjee. Thoracic Surgery Research Laboratory, Division of Thoracic Surgery, The Toronto Hospital, University of Toronto, Canada, M5G 2C4.

Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine that has recently been suggested to have protective activity against both the oxidative injury of ischemia-reperfusion and the destructive damage of chronic rejection in lung transplantation. In a lead up to therapeutic studies using the IL-10 gene, the transfection efficacy of a replication-deficient adenoviral vector expressing human IL-10 was investigated. To assess optimal dosing, three dosages of the vector-gene construct were administered to rats by intramuscular injection. Human IL-10 transgene expression was measured from plasma samples on days 1, 7, and 14 post-injection. Results showed a dose-dependent pattern of expression, with peak levels at day 1 and declining levels thereafter. These findings demonstrate that intramuscular adenoviral IL-10 gene transfer provides measurable levels of transgene expression in plasma. The rat model of adenoviral-mediated IL-10 gene transfer, thus characterized, provides the basis for further investigation into the physiological effects and therapeutic potential of IL-10 in an *in vivo* lung transplantation model.

RE2

ACCELERATED CARBON MONOXIDE ELIMINATION DURING NORMOCARBIC HYPERPNEA J.A.Fisher, L.Z.Sommer*, J. Rucker, A.Veseley, E.Levine, Y.Greenwald, G.Vogyesi, L.Fedorko, S.Iscoe Department of Anaesthesia, Faculty of Medicine, University of Toronto, Toronto, Canada.

Background: The major impediment to the use of hyperventilation in the treatment of CO poisoning is the development of respiratory alkalosis. Using a recently described circuit that passively prevents hypocarbia during hyperpnea, we examined the effect of hyperpnea on the rate of elimination of carboxyhaemoglobin (COHb) in anaesthetized dogs. **Methods:** Seven pentobarbital-anaesthetized ventilated dogs were exposed to CO and then ventilated with room air at normocarbia (control). Five were then ventilated with 100% O_2 at control and six times control ventilation for 42 min each. Two were placed in a hyperbaric chamber and treated at 2.8 ATA according to a standard protocol. We monitored blood gases and the rate of COHb elimination. **Results:** The control half time ($t_{1/2}$) for elimination of COHb was 212 ± 17.3 (SD) min. On 100% O_2, $t_{1/2}$ decreased to 42 ± 3 min at control ventilation, 18 ± 2 min at six times control ventilation and 24 min with hyperbaric O_2. During hyperpnea, arterial PCO_2 rose on average by 5.0 mmHg. **Conclusion:** In anaesthetized ventilated dogs, normocarbic hyperpnea accelerated the rate of COHb elimination to an extent comparable to hyperbaric O_2. This method can provide a readily accessible treatment for CO poisoning, alone or in addition to hyperbaric O_2.

Rheumatology

RH1

A CRITICAL APPRAISAL OF THE QUALITY OF OBSERVATIONAL STUDIES REPORTING TERMINATION RATES OF SELECTED ANTI-RHEUMATIC AGENTS. Anita Wong*, Andreas Maetzel, Claire Bombardier Wellesley Hospital Research Institute, Toronto, Ontario, Canada

Objective: Observational studies of rheumatoid arthritis (RA) patients under routine clinical care offer valuable information on the effectiveness of anti-rheumatic agents. Important long-term outcomes, such as treatment termination rates, will be closer to reality and are often not observed in randomized controlled clinical trials. We undertook a critical appraisal of the comprehensiveness of reporting of termination rates in published observational studies.

Methods: A Medline search using MeSH terms and textwords was conducted to retrieve all articles published between 1966 and 1997 dealing with the following therapies for RA: methotrexate (MTX), gold sodium aurothiomalate (GST), hydroxychloroquine (HCQ) and sulfasalazine (SSZ). All observational studies providing information on termination rates were assessed using a set of methodologic criteria.

Results: There were 88 studies with 111 treatment arms providing information on termination rates: MTX-48, GST-45, HCQ-8, and SSZ-10. The reporting of termination rates was a primary objective in 42 of these 88 studies; patient status was ascertained retrospectively in 26 studies and prospectively in 62. Long-term outcomes such as response to treatment were defined by explicit criteria in only 21 (26%) studies, of which 17 were prospective. In 50 studies there was a variable length of follow-up for individual patients requiring them to be classified as censored at the end of the observation period; lifetable or Kaplan Meier survival analysis techniques were applied in 26 (52%) of these studies. Information that is crucial to understand these studies, such as the number of patients at risk, censored, as well as terminating treatment at major study intervals was reported in only 13, 4 and 7 studies respectively.

Conclusion: Long-term observational studies provide important information about the effectiveness of therapeutic agents, however there is no consistency in the reporting of treatment termination rates and the use of criteria for patient improvement. Therapeutic success should be defined explicitly in all future long-term observational studies; common reporting standards should be adopted to enable comparison among studies.

RH2

EFFECTS OF GLUCOSAMINE HYDROCHLORIDE IN RELIEVING PAIN AND IMPROVING FUNCTION IN PATIENTS WITH OSTEOARTHRITIS (OA) OF THE KNEE: AN OPEN TRIAL. C.R. Wein*, J.B. Houpt. Rheumatic Disease Unit, Mount Sinai Hospital, University of Toronto, Canada, M5G 1X5.

Osteoarthritis (OA) is a degenerative disease that involves chondrocyte and matrix changes resulting in loss of articular cartilage structure and function accompanied by attempted cartilage repair and bone remodelling. Studies from Europe have suggested that glucosamine sulfate, an amine sugar derived from the chitin of crustaceans, is able to reduce the pain of OA. Glucosamine is part of the naturally occurring linear polymer carbohydrate glycosaminoglycan, a building block of the proteoglycans found in cartilage. A double blind, randomized, placebo-controlled trial studying the effects of glucosamine hydrochloride (a different salt) on reduction of pain and disability of OA of the knee is currently under way. 100 subjects are randomized to receive glucosamine hydrochloride or placebo. Following the 10-week double blind trial, subjects are given a 2-month supply of open label glucosamine hydrochloride. This abstract details the telephone survey of patients at 4 and 8 weeks following the open label. Patients were asked if they believe that they were on placebo or active agent in the closed trial and if they believed that they were better, the same or worse with regard to pain and function at the end of the closed trial compared to the beginning. Patients were interviewed with regards to compliance, analgesic use, pain and function. The data for the closed and open trial will be analyzed in a blinded fashion. We hope to determine if the glucosamine hydrochloride is useful for the pain of osteoarthritis of the knee and whether a prolonged period of use is required for efficacy.

RH3

DASH CORRELATES WITH MEASURES OF CLINICAL FUNCTION IN PSORIATIC ARTHRITIS. **A. NAVSARIKAR*, D. GLADMAN. Centre for Prognostic Studies in Rheumatic Diseases, University of Toronto, Canada.**

Psoriatic arthritis (PsA) is an inflammatory arthritis associated with psoriasis and may affect as much as 1% of the population. Joint deformity, disability and destruction are frequent among these patients. The patients' perception of their functional ability is an important aspect of assessing and monitoring the patient's disease status and adjusting treatment. The DASH (Disabilities of Arm, Shoulder, and Hand) was developed as an evaluative outcome measure for patients with upper extremity musckuloskeletal conditions. Our purpose was to determine whether patient perception of their functional ability correlates with clinical involvement in patients with PsA. ***Methods.*** Patients were asked to complete a 30-item DASH questionnaire during their clinic visits. The DASH yields a single number score ranging from 0 to 100 for this instrument, with zero reflecting good function. Clinical assessments were performed according to a standard protocol including number of actively inflamed joints (joints with stress pain and/or effusions), total number of damaged joints, grip strength (measured in mm Hg using sphygmomanometer in right and left hands). Spearman rank correlations were calculated between clinical measures and the DASH.

Results. Fifty consecutive patients were studied in this prospective study. The DASH score correlated with clinical measures of function including right grip strength ($r = -0.47$, CI -0.67, -0.21), American College of Rheumatology functional class ($r = 0.45$, CI 0.19, 0.65) and number of active joints ($r = 0.40$, CI 0.14, 0.61). The DASH had a higher correlation with active joints in the upper limbs ($r = 0.65$, CI 0.46, 0.79) than with (total) number of active joints. ***Discussion.*** Our study demonstrates that the DASH questionnaire correlates with measures of clinical function in PsA. Furthermore, since the DASH has a very high correlation with active joints in the upper extremity, this validates its use for assessment of patient perception of their functional ability in the upper extremity. Consequently, our data suggests that the DASH may be a good tool for the self-assessment of PsA patients of their functional ability in their upper extremity.

Surgery

SU1

PREDICTIVE FACTORS IN ARTHROSCOPIC SUBACROMIAL DECOMPRESSION. P.J.Alexander*, R.M.Holtby. Orthopedic and Arthritic Hospital, 43 Wellesley St. East, Suite 634, Toronto On, M4Y 1H1

INTRODUCTION: The purpose of this study is to determine which factors in the pre-operative history, physical examination, radiological and operative findings influence the results of arthroscopic subacromial decompression.

METHODS: In this cohort study, 87 patients (35 females, 52 males) were prospectively analyzed and retrospectively reviewed. They were followed at regular intervals up to one year post-op. A total of 91 shoulders were operated on (4 patients had bilateral operations). The primary outcome measure was the one year post-operative UCLA score.

Plots of dependent versus independent variables were used to determine the strength of linear relationships. Pearson correlation analysis was used to determine any significant correlation between these variables. A multiple regression analysis was also performed to determine what factors influenced the final outcome.

RESULTS: The mean UCLA score changed from 15.6 (out of 35) pre-operatively to 26.5 post-operatively at one year. The results regarding the efficacy of the procedure were consistent with those reported in the literature. The Pearson correlation analysis found the following to be significant predictive factors: no significant injury (1 year UCLA score = 23.52) versus significant injury (21.05), normal external rotation power (27.15) compared with external rotation weakness (16.29), and presence of partial thickness (20.7) versus full thickness tear (28.35). Multiple regression analysis indicated that low UCLA score, presence of full thickness tear, heavy manual labor and presence of significant injury were all predictors of a poorer outcome. These variables accounted for 46% of the variation in response. The overall model was highly significant (p=0.0001).

DISCUSSION AND CONCLUSION: In a series of patients treated with acromioplasty, results consistent with the literature were obtained. Factors predicting a poor result include: significant injury, external rotation weakness, full thickness cuff tears, low UCLA scores and work involving heavy manual labor.

SU2

HEALTH RELATED QUALITY OF LIFE FOLLOWING FRESH OSTEOCHONDRAL ALLOGRAFTS IN THE KNEE: A MINIMUM 5 YEAR FOLLOW-UP. J. Stimec*, J. Krajbich, Z. Agnidis, C. Hutchison, A.E. Gross. Department of Orthopaedic Surgery, Mount Sinai Hospital and University of Toronto, Canada.

Fresh osteochondral allografts (OCA) are used to reconstruct defects of bone and articular cartilage of the knee. To date, patient perceptions of their health related quality of life have not been reported. The purpose of this study was to evaluate the long term outcomes of patient perceived health status following fresh OCA transplanted greater than 5 years ago.

This is a retrospective study of 58 patients with 59 fresh OCA. The three health status questionnaires used were: The WOMAC, the Toronto Extremity Salvage Score (TESS), SF-36. Surgical variables included: type, incidence and time to post-operative complications, graft types and site, number of previous knee operations, underlying etiology and realignment.

There were 33 males and 25 females with the average age of 35 years at the time of surgery. Eight-eight percent of grafts were unipolar with 43% of grafts at the lateral tibial plateau, 19% lateral femoral condyles and 15% medial femoral condyles. Forty-seven percent of patients had least one knee surgery prior to transplantation.

Patients demonstrated lower scores in comparison with normative values of the SF-36, across all 8 subscales. When the fresh OCA patients were divided into two groups; 5-10 years post surgery and 10 or more years post surgery, there was no significant difference in outcome. A moderate to high association was noted between the SF-36 physical function subscale and the TESS and WOMAC scores (Kendall Tau-B ranges, .46 to .73). Among surgical variables, a moderate association was observed between bipolar procedures and the incidence of complications (Kendall Tau-B = .41). Patients with bipolar procedures had statistically significant lower scores in all three functional outcome measures compared with unipolar procedures.

To summarize, 94% of patients reported some degree of success in relieving pain and restoring function. Findings suggest that patients with unipolar procedures may have an advantage over bipolar with respect to the incidence of complications and higher levels of physical function.

SU3

THE INFLUENCE OF NUMBER OF CORTICES ON THE STIFFNESS OF PLATE FIXATION OF DIAPHYSEAL FRACTURES. M. T. Nousiainen*, A. W. ElMaraghy, E. H. Schemitsch. Division of Orthopaedic Surgery, St. Michael's Hospital, University of Toronto, Ontario, Canada M5C 1R6.

This study determined the biomechanical influence of number of cortices of purchase on the bending and torsional stiffness of two common types of diaphyseal plate fixation, dynamic compression (DCP) and limited contact dynamic compression (LC-DCP). Paired straight diaphyseal segments of canine radii were used to test two groups fixed with either DCP or LC-DCP. One member of each pair was tested intact as a control, while the other was tested sequentially with 5 to 10 cortices of fixation on either side of a transverse osteotomy produced by an oscillating saw. Normalized stiffness in torsion and 4-point bending for each construct were determined in the elastic range using a model TTCM Instron materials testing machine. For both groups, there was a significant increase in torsional stiffness when going from an odd number of cortices to the next even number of cortices, but there was no difference going from an even number of cortices to the next odd number of cortices. Compared to intact controls, the mean torsional stiffness of the 5 cortices construct was 71% for DCP and 60% for LC-DCP; for the 10 cortices construct, it was 100% for DCP and 99% for LC-DCP. Compared to intact controls, the mean bending stiffness for the 5 cortices construct was 142% for DCP and 92% for LC-DCP; for the 10 cortices construct, it was 192% for DCP and 182% for LC-DCP. There was no significant difference in the bending or torsional stiffness between the DCP and LC-DCP groups for any construct. The results of this study suggest that (1) bicortical screws provide a biomechanical advantage over unicortical screws and (2) bending and torsional stiffness approaches that of intact bone with longer (10-hole) plates. Choice of plate length in diaphyseal fracture fixation should therefore consider the benefits of stability versus potentially harmful soft tissue stripping.

SU4

FRACTURES OF THE MANDIBULAR CONDYLE: A RETROSPECTIVE ANALYSIS OF 65 PATIENTS. K.M. Horton*, C.R. Forrest. Division of Plastic Surgery, Sunnybrook Health Science Centre, University of Toronto, Canada, M4N 3M5.

INTRODUCTION: The condylar neck is the commonest site for fractures of the mandible to occur, being present in up to 36% of all mandibular fractures. Both surgical (open reduction and internal plate fixation) and non-surgical methods of treatment have been advocated with advantages demonstrated in both areas, but with no clear guidelines as to the optimal form of management. The purpose of this study was to perform a retrospective outcome analysis on patients seen a Level I trauma centre with mandibular fractures involving the condyle or condylar neck region, in order to help determine practice guidelines and the optimum method of management to treat these injuries.

MATERIALS AND METHODS: Patients admitted to Sunnybrook Health Science Centre between 1992-1997 with condyle/condylar neck fractures were enrolled in the study. Data was obtained from a prospectively-gathered data-base, chart review, patient recall and questionnaire. In addition, a similar data profile was collected on patients with mandibular fractures in sites other than the condyle/condylar neck region for comparison. Patients excluded from this study consisted of gun-shot wounds, penetrating trauma or significant bone loss in the region of the condyle.

RESULTS: A total of 65 patients (49 males; 16 females; mean age = 38 yrs) were identified with condylar neck fractures with a mean follow-up of 13 weeks. Unilateral injuries were present in 53 patients (39 with other mandible fractures), and bilateral injuries in 12 patients (9 with other mandible fractures). 62 patients underwent closed reduction and intermaxillary fixation (2-3 weeks) and 3 patients underwent open reduction/internal fixation within 4 days (range 1-11 days). Associated injuries were present in 71% of patients (head injury: 40%, extremity: 34%, chest: 18%, abdomen: 11%, c-spine: 2%). At this time, 10 (16%) patients have been available for recall and questionnaire. Details regarding the outcome of these patients in terms of morbidity and continued symptoms will be analyzed and presented. Additional data is forthcoming. This data will be compared to 54 patients sustaining mandibular fractures in regions other than the condylar neck.

CONCLUSIONS: Controversy exists regarding the optimal method of management of mandibular fractures involving the condyle/condylar neck region. It is hoped that the data collected from this study will contribute to the body of knowledge regarding the optimal method of treatment for these fractures.

SU5

RISK FACTORS FOR RECURRENCE OF CD FOLLOWING ILEO-CAECAL RESECTION, **D. Moskovitz*; R.S. McLeod, MD; G. Greenberg, MD and Z. Cohen, MD. Division of General Surgery, Department of Surgery, Faculty of Medicine, Mount Sinai Hospital, University of Toronto, Canada, M5G 1X5**

Introduction: A retrospective study was performed to determine post-operative recurrence rates and risk factors for recurrence in a defined population following ileo-caecal resection for Crohn's disease. **Methods:** 95 patients underwent ileo-caecal resection. There were 48 males and 47 females; mean age at initial surgery was 31.8 ± 12.5 years. In all patients this was their first operation. Recurrence was defined as symptomatic (confirmed by endoscopy and radiology) or operative (requiring further surgery). Risk factors for recurrence were: operative technique (hand-sewn vs. stapled anastomosis); post-operative smoking patterns and pre-operative steroid usage. Univariate analyses were performed using a Cox proportion regression model while adjusting for age of onset. **Results:** 53 patients recurred symptomatically with a mean follow-up time from first surgery of 89.8 ± 57.4 months. Of these 24 required surgery (operative recurrence). Life table analysis showed the following.

Years to Recurrence	Symptomatic Group	Operative Group
1	15	6
2	31	14
3	45	22

Smoking was a highly significant risk factor for those who recurred operatively (p = 0.0029). Surgical technique (hand-sewn vs. stapled) and steroid usage were not statistically significant. **Discussion:** This retrospective study demonstrates symptomatic recurrence rates similar to those reported prospectively. The type of anastomosis and preoperative steroid use do not affect recurrence. However, patients who continue to smoke post-operatively are at significantly higher risk. Therefore these patients should be encouraged to stop smoking.

SU6

OUTCOME OF KIDNEY TRANSPLANT ALONE (KTA) VERSUS SYNCHRONOUS PANCREAS-KIDNEY TRANSPLANTION (SPK) IN TYPE 1 DIABETICS. C Rowsell, MS Cattral, Multiorgan Transplant Programme, The Toronto Hospital, University of Toronto, Canada, M5G 2C4.

Although SPK is an alternative to KTA for patients with endstage diabetic nephropathy, concern continues to exist about the increased morbidity and mortality of SPK. To address this issue, we analysed the outcome of 59 consecutive type 1 diabetics who received KTA from living related (LRD) or cadaveric (CAD) donors and SPK between Jan 1993 and July 1997. All 3 groups were similar with respect to age, duration of diabetes, daily insulin dose, HbAlc, and cardiovascular comorbidity. They differed with respect to mean (± SD) duration of dialysis (SPK, 23± 15 mo; KTA-LRD, 11± 8; KTA-CAD, 33±14), and HLA mismatch (SPK, 5.1±0.8, KTA-LRD, 2.2 ±1.5, and KTA-CAD, 3.5±1.6). Maintenance immunosuppression consisted of Neoral, prednisone, and imuran.

RESULTS	SPK	KTA-LRD	KTA-CAD	P
Follow-up(mo.)	11±6	29±16	24±16	0.001
Survival -Patient	19/20(95%)	20/20(100%)	16/19(84%)	NS
Kidney	19/20(95%)	19/20(95%)	16/19(84%)	NS
Pancreas	18/20(90%)	-	-	-
Need for Dialysis after Tx	0(0%)	2(10%)	9(45%)	0.001
Acute Rejection during 1st yr.	5(26%)	7(35%)	9(47%)	NS
OKT3 Rescue	3(16%)	4(20%)	2(11%)	NS
Reoperation	2(10%)	2(10%)	3(16%)	NS
Major Infection	8(42%)	5(25%)	7(37%)	NS
Hospitalization -Initial	15±3	17±11	17±7	NS
(days) Total 1st year	24±10	22±13	29±17	NS
Serum Creat. 1 mo. (umol/L)	140±32	165±114	186±125	NS

Our data indicates that graft function, morbidity, and mortality of SPK does not significantly differ from LRD- or CAD-KTA. Since SPK offers the additional benefit of insulin-independence, we conclude that it is an excellent treatment option for well-selected patients.

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